



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/JP99/03242 (22) International Filing Date: 18 June 1999 (18.06.99) (30) Priority Data: 10/180008 26 June 1998 (26.06.98) JP (71) Applicants (for all designated States except US): SAGAMI CHEMICAL RESEARCH CENTER [JP/JP]; 4-1, Nishi-Ohnuma 4-chome, Sagamihara-shi, Kanagawa 229-0012 (JP). PROTEGENE INC. [JP/JP]; 2-20-3, Naka-cho., Meguro-ku, Tokyo 153-0065 (JP). (72) Inventors; and (75) Inventors/Applicants (for US only): KATO, Seishi [JP/JP]; 3-46-50, Wakamatsu, Sagamihara-shi, Kanagawa 229-0014 (JP). KIMURA, Tomoko [JP/JP]; 302, 4-1-28, Nishiikuta, Tama-ku, Kawasaki-shi, Kanagawa 214-0037 (JP). (74) Agents: AOYAMA, Tamotsu et al.; Aoyama & Partners, IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi, Osaka 540-0001 (JP).		(81) Designated States: AU, CA, JP, MX, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> (88) Date of publication of the international search report: 20 April 2000 (20.04.00)
(54) Title: HUMAN PROTEINS HAVING HYDROPHOBIC DOMAINS AND DNAS ENCODING THESE PROTEINS		
(57) Abstract A human protein having a hydrophobic domain and comprising any of the amino acid sequences represented by Sequence Nos. 1 to 10, a cDNA coding for said protein, and an expression vector comprising the cDNA as well as an eucaryotic cell comprising the cDNA. The protein can be provided by expression of the cDNA coding for such protein.		

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-6 partially

A protein comprising the amino acid sequence SEQ ID NO 1, a DNA SEQ ID NO 11 or 21, encoding this protein, as well as an expression vector capable of expressing this sequence and a eukaryotic cell expressing the DNA

2. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 2 and DNA SEQ ID 12 and 23

3. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 3 and DNA SEQ ID 13 and 25

4. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 4 and DNA SEQ ID 14 and 27

5. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 5 and DNA SEQ ID 15 and 29

6. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 6 and DNA SEQ ID 16 and 31

7. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 7 and DNA SEQ ID 17 and 33

8. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 8 and DNA SEQ ID 18 and 35

9. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 9 and DNA SEQ ID 19 and 37

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

10. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 10 and
DNA SEQ ID 20 and 39

INTERNATIONAL SEARCH REPORT

Information on patent family members

Application No

PCT/JP 99/03242

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9821328 A	22-05-1998	AU 4885297 A	03-06-1998
		EP 0941320 A	15-09-1999

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EE	Estonia						

INTERNATIONAL SEARCH REPORT

Patent Application No

PCT/JP 99/03242

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K14/705 C12N5/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 98 21328 A (KATO SEISHI ; PROTEGENE INC (JP); SEKINE SHINGO (JP); SAGAMI CHEM R) 22 May 1998 see abstract see page 17, last paragraph - page 18, paragraph 1</p> <p style="text-align: center;">--- -/--</p>	1-6

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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- *O* document referring to an oral disclosure, use, exhibition or other means
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Date of the actual completion of the international search

20 October 1999

Date of mailing of the international search report

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Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/JP 99/03242

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE EMBL Accession Number N94214, 19 April 1996 HILLIER L ET AL: "za27c03.r1 Homo sapiens cDNA clone 293764 5' similar to PIR:A54313 androgen-regulated protein FAR-17 - golden hamster" XP002119529 cited in the application 97.8% identity in 357 BP overlap with SEQ ID 11 see page 17, last paragraph - page 18, paragraph 1</p>	1-6
A	<p>--- D'ANDREA ET AL: "Molecular Cloning of NKBL. A Natural Killer Cell Receptor for HLA -B Allotypes" JOURNAL OF IMMUNOLOGY, vol. 155, no. 5, 1 September 1995, pages 2306-2310 2310, XP002111500 see abstract paragraph 1 see page 2307, right-hand column, line 16 - paragraph 1</p>	1-6
A	<p>--- GILLEN C M ET AL: "Molecular cloning and functional expression of the K-Cl cotransporter from rabbit, rat, and human." JOURNAL OF BIOLOGICAL CHEMISTRY., vol. 271, no. 27, 5 July 1996, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD., US, pages 16237-16244, XP002119528 see abstract paragraph 1</p>	1-6
A	<p>--- KYTE J ET AL: "A SIMPLE METHOD FOR DISPLAYING THE HYDROPATHIC CHARACTER OF A PROTEIN" JOURNAL OF MOLECULAR BIOLOGY, vol. 157, no. 1, 5 May 1982, pages 105-132, XP000609692 cited in the application see the whole document paragraph 1</p>	1-6
P,X	<p>--- DATABASE EMBL Accession Number AF151861, 1 June 1999 LIN C W: "Homo sapiens CGI-103 protein mRNA, complete cds." XP002119530 99.4% identity in 699 BP overlap with SEQ ID 11 see the whole document paragraph 1</p> <p>--- -/--</p>	1-6

INTERNATIONAL SEARCH REPORT

Application No
PCT/JP 99/03242

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	<p>DATABASE EMBL Accession Number AF153605, 30 June 1999 KIM M K ET AL: "Homo sapiens androgen induced protein (AIG-1) mRNA, complete cds." XP002119531 99.7% identity in 714 BP overlap with SEQ ID NO 11 see the whole document paragraph 1 -----</p>	1-6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 99/03242

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
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1-6 (partially), see additional sheet, subject 1.

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07K	A2	(11) International Publication Number: WO 00/00506 (43) International Publication Date: 6 January 2000 (06.01.00)
<p>(21) International Application Number: PCT/JP99/03242</p> <p>(22) International Filing Date: 18 June 1999 (18.06.99)</p> <p>(30) Priority Data: 10/180008 26 June 1998 (26.06.98) JP</p> <p>(71) Applicants (for all designated States except US): SAGAMI CHEMICAL RESEARCH CENTER [JP/JP]; 4-1, Nishi-Ohnuma 4-chome, Sagamihara-shi, Kanagawa 229-0012 (JP). PROTEGENE INC. [JP/JP]; 2-20-3, Naka-cho., Meguro-ku, Tokyo 153-0065 (JP).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): KATO, Seishi [JP/JP]; 3-46-50, Wakamatsu, Sagamihara-shi, Kanagawa 229-0014 (JP). KIMURA, Tomoko [JP/JP]; 302, 4-1-28, Nishiikuta, Tama-ku, Kawasaki-shi, Kanagawa 214-0037 (JP).</p> <p>(74) Agents: AOYAMA, Tamotsu et al.; Aoyama & Partners, IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi, Osaka 540-0001 (JP).</p>		<p>(81) Designated States: AU, CA, JP, MX, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>Without international search report and to be republished upon receipt of that report.</i></p>
<p>(54) Title: HUMAN PROTEINS HAVING HYDROPHOBIC DOMAINS AND DNAS ENCODING THESE PROTEINS</p> <p>(57) Abstract</p> <p>A human protein having a hydrophobic domain and comprising any of the amino acid sequences represented by Sequence Nos. 1 to 10, a cDNA coding for said protein, and an expression vector comprising the cDNA as well as an eucaryotic cell comprising the cDNA. The protein can be provided by expression of the cDNA coding for such protein.</p>		

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DESCRIPTION

HUMAN PROTEINS HAVING HYDROPHOBIC
DOMAINS AND DNAs ENCODING THESE PROTEINS

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TECHNICAL FIELD

The present invention relates to human proteins having hydrophobic domains, DNAs coding for these proteins, and expression vectors of these DNAs as well as eucaryotic cells expressing these DNAs. The proteins of the present invention can be employed as pharmaceuticals or as antigens for preparing antibodies against these proteins. The human cDNAs of the present invention can be utilized as probes for the gene diagnosis and gene sources for the gene therapy. Furthermore, the cDNAs can be utilized as gene sources for large-scale production of the proteins encoded by these cDNAs. Cells, wherein these membrane protein genes are introduced to express secretory proteins and membrane proteins in large amounts, can be utilized for detection of the corresponding receptors and ligands, screening of novel low-molecular pharmaceuticals, and so on.

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BACKGROUND ART

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Cells secrete many proteins outside the cells. These secretory proteins play important roles for the proliferation control, the differentiation induction, the material transportation, the biological protection, etc. in the cells. Different from intracellular proteins, the secretory proteins exert their actions outside the cells, whereby they can be administered in the intracorporeal manner such as the injection or the drip, so that there

are hidden potentialities as medicines. In fact, a number of human secretory proteins such as interferons, interleukins, erythropoietin, thrombolytic agents, etc. have been currently employed as medicines. In addition, secretory proteins other than those described above have been undergoing clinical trials to develop as pharmaceuticals. Because it has been conceived that the human cells still produce many unknown secretory proteins, availability of these secretory proteins as well as genes coding for them is expected to lead to development of novel pharmaceuticals utilizing these proteins.

On the other hand, membrane proteins play important roles, as signal receptors, ion channels, transporters, etc. in the material transportation and the information transmission which are mediated by the cell membrane. Examples thereof include receptors for a variety of cytokines, ion channels for the sodium ion, the potassium ion, the chloride ion, etc., transporters for saccharides and amino acids, and so on, where the genes of many of them have been cloned already. It has been clarified that abnormalities of these membrane proteins are associated with a number of hitherto-cryptogenic diseases. Therefore, discovery of a new membrane protein is anticipated to lead to elucidation of the causes of many diseases, so that isolation of a new gene coding for the membrane protein has been desired.

Heretofore, owing to difficulty in the purification, these secretory proteins and membrane proteins have been isolated by an approach from the gene side. A general method is the so-called expression cloning which comprises transfection of a cDNA library in eucaryotic cells to express cDNAs and then screening of the cells expressing

the target active protein by secretion or on the surface of membrane. However, this method is applicable only to cloning of a gene of a protein with a known function.

In general, secretory proteins and membrane proteins possess at least one hydrophobic domain inside the proteins, wherein, after synthesis thereof in the ribosome, this domain works as a secretory signal or remains in the phospholipid membrane to be trapped in the membrane. Accordingly, the evidence of this cDNA for encoding the secretory proteins and the membrane protein is provided by determination of the whole base sequence of a full-length cDNA followed by detection of highly hydrophobic domains in the amino acid sequence of the protein encoded by this cDNA.

DISCLOSURE OF INVENTION

The object of the present invention is to provide novel human proteins having hydrophobic domains, DNAs coding for these proteins, and expression vectors of these DNAs as well as transformation eucaryotic cells that are capable of expressing these DNAs.

As the result of intensive studies, the present inventors have been successful in cloning of cDNAs coding for proteins having hydrophobic domains from the human full-length cDNA bank, thereby completing the present invention. In other words, the present invention provides human proteins having hydrophobic domains, namely proteins containing any of the amino acid sequences represented by Sequence Nos. 1 to 10. Moreover, the present invention provides DNAs coding for the above-mentioned proteins, exemplified by cDNAs containing any of the base sequences represented by Sequence Nos. 11 to 21, 23, 25, 27, 29, 31,

33, 35, 37 and 39, as well as expression vectors that are capable of expressing any of these DNAs by in vitro translation or in eucaryotic cells and transformation eucaryotic cells that are capable of expressing these DNAs and of producing the above-mentioned proteins.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP00631.

Fig. 2 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02403.

Fig. 3 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02420.

Fig. 4 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10349.

Fig. 5 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10508.

Fig. 6 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10524.

Fig. 7 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10529.

Fig. 8 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10537.

Fig. 9 A figure depicting the

hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10549.

Fig. 10 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10551.

BEST MODE FOR CARRYING OUT THE INVENTION

The proteins of the present invention can be obtained, for example, by a method for isolation from human organs, cell lines, etc., a method for preparation of peptides by the chemical synthesis, or a method for production with the recombinant DNA technology using the DNAs coding for the hydrophobic domains of the present invention, wherein the method for obtainment by the recombinant DNA technology is employed preferably. For instance, in vitro expression of the proteins can be achieved by preparation of an RNA by in vitro transcription from a vector having one of cDNAs of the present invention, followed by in vitro translation using this RNA as a template. Also, recombination of the translation region into a suitable expression vector by the method known in the art leads to expression of a large amount of the encoded protein by using prokaryotic cells such as *Escherichia coli*, *Bacillus subtilis*, etc., and eucaryotic cells such as yeasts, insect cells, mammalian cells, etc.

In the case in which one of the proteins of the present invention is produced by expressing the DNA by in vitro translation, the protein of the present invention can be produced in vitro, when the translation region of this cDNA is subjected to recombination to a vector having an RNA polymerase promoter, followed by addition to an in vitro translation system such as a rabbit reticulocyte

lysate or a wheat germ extract, containing an RNA polymerase corresponding to the promoter. RNA polymerase inhibitors are exemplified by T7, T3, SP6, and the like. The vectors containing these RNA polymerase inhibitors are exemplified by pKA1, pCDM8, pT3/T7 18, pT7/3 19, pBluescript II, and so on. Furthermore, a membrane protein of the present invention can be expressed as the form incorporated in the microsome membrane, when a canine pancreas microsome or the like is added into the reaction system.

In the case in which a protein of the present invention is produced by expressing the DNA using a microorganism such as *Escherichia coli* etc., a recombinant expression vector bearing the translation region in the cDNA of the present invention is constructed in an expression vector having an origin, a promoter, a ribosome-binding site, a cDNA-cloning site, a terminator etc., which can be replicated in the microorganism, and, after transformation of the host cells with this expression vector, the thus-obtained transformant is incubated, whereby the protein encoded by said cDNA can be produced on a large scale in the microorganism. In this case, a protein fragment containing an optional region can be obtained by carrying out the expression with inserting an initiation codon and a termination codon in front of and behind an optional translation region. Alternatively, a fusion protein with another protein can be expressed. Only a protein portion coding for this cDNA can be obtained by cleavage of this fusion protein with a suitable protease. The expression vector for *Escherichia coli* is exemplified by the pUC system, pBluescript II, the pET expression system, the pGEX expression system, and so

on.

In the case in which one of the proteins of the present invention is produced by expressing the DNA in eucaryotic cells, the protein of the present invention can be obtained by secretory production or produced as a membrane protein on the cell-membrane surface, when the translation region of this cDNA is subjected to recombination to an expression vector for eucaryotic cells that has a promoter, a splicing region, a poly(A) insertion site, etc., followed by introduction into the eucaryotic cells. The expression vector is exemplified by pKA1, pED6dpc2, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, EBV vector, pRS, pYES2, and so on. Examples of eucaryotic cells to be used in general include mammalian culture cells such as simian kidney cells COS7, Chinese hamster ovary cells CHO, etc., budding yeasts, fission yeasts, silkworm cells, *Xenopus laevis* egg cells, and so on, but any eucaryotic cells may be used, provided that they are capable of expressing the present proteins. The expression vector can be introduced in the eucaryotic cells by methods known in the art such as the electroporation method, the potassium phosphate method, the liposome method, the DEAE-dextran method, and so on.

After one of the proteins of the present invention is expressed in prokaryotic cells or eucaryotic cells, the objective protein can be isolated from the culture and purified by a combination of separation procedures known in the art. Such examples include treatment with a denaturing agent such as urea or a surface-active agent, sonication, enzymatic digestion, salting-out or solvent precipitation, dialysis, centrifugation, ultrafiltration, gel filtration, SDS-PAGE, isoelectric focusing, ion-

exchange chromatography, hydrophobic chromatography, affinity chromatography, reverse phase chromatography, and so on.

5 The proteins of the present invention include peptide fragments (more than 5 amino acid residues) containing any partial amino acid sequence in the amino acid sequences represented by Sequence Nos. 1. to 10. These peptide fragments can be utilized as antigens for preparation of antibodies. Hereupon, among the proteins of the present
10 invention, those having the signal sequence are secreted in the form of maturation proteins on the surface of the cells, after the signal sequences are removed. Therefore, these maturation proteins shall come within the scope of the present invention. The N-terminal amino acid sequences
15 of the maturation proteins can be easily identified by using the method for the cleavage-site determination in a signal sequence [Japanese Patent Kokai Publication No. 1996-187100]. Furthermore, some membrane proteins undergo the processing on the cell surface to be converted to the
20 secretory forms. Such proteins or peptides in the secretory forms shall come within the scope of the present invention. In the case where sugar chain-binding sites are present in the amino acid sequences, expression in appropriate eucaryotic cells affords proteins wherein
25 sugar chains are added. Accordingly, such proteins or peptides wherein sugar chains are added shall come within the scope of the present invention.

The DNAs of the present invention include all DNAs coding for the above-mentioned proteins. These DNAs can be
30 obtained by using a method by chemical synthesis, a method by cDNA cloning, and so on.

The cDNAs of the present invention can be cloned, for

example, from cDNA libraries of the human cell origin. These cDNA are synthesized by using as templates poly(A)⁺ RNAs extracted from human cells. The human cells may be cells delivered from the human body, for example, by the operation or may be the culture cells. The cDNAs can be synthesized by using any method selected from the Okayama-Berg method [Okayama, H. and Berg, P., Mol. Cell. Biol. 2: 161-170 (1982)], the Gubler-Hoffman method [Gubler, U. and Hoffman, J. Gene 25: 263-269 (1983)], and so on, but it is preferred to use the capping method [Kato, S. et al., Gene 150: 243-250 (1994)], as exemplified in Examples, in order to obtain a full-length clone in an effective manner. In addition, commercially available, human cDNA libraries can be utilized. Cloning of the cDNAs of the present invention from the cDNA libraries can be carried out by synthesis of an oligonucleotide on the basis of an optional portion in the cDNA base sequences of the present invention, followed by screening using this oligonucleotide as the probe according to the colony or plaque hybridization by a method known in the art. In addition, the cDNA fragments of the present invention can be prepared by synthesis of an oligonucleotide to be hybridized at both termini of the objective cDNA fragment, followed by the usage of this oligonucleotide as the primer for the RT-PCR method from an mRNA isolated from human cells.

The cDNAs of the present invention are characterized by containing either of the base sequences represented by Sequence Nos. 11 to 20 or the base sequences represented by Sequence Nos. 21, 23, 25, 27, 29, 31, 33, 35, 37 and 39. Table 1 summarizes the clone number (HP number), the cells affording the cDNA, the total base number of the cDNA, and the number of the amino acid residues of the encoded

protein, for each of the cDNAs.

Table 1

Sequence No.	HP number	Cells	Base number	Number of amino acid residues
1, 11, 21	HP00631	Saos-2	1085	238
2, 12, 23	HP02403	Stomach cancer	1168	194
3, 13, 25	HP02420	Stomach cancer	624	139
4, 14, 27	HP10349	Stomach cancer	1121	323
5, 15, 29	HP10508	Stomach cancer	827	231
6, 16, 31	HP10524	Stomach cancer	1189	97
7, 17, 33	HP10529	Saos-2	1500	198
8, 18, 35	HP10537	Saos-2	806	140
9, 19, 37	HP10549	Stomach cancer	1718	201
10, 20, 39	HP10551	Stomach cancer	995	249

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Hereupon, the same clones as the cDNAs of the present invention can be easily obtained by screening of the cDNA libraries constructed from the human cell lines and human tissues utilized in the present invention by the use of an oligonucleotide probe synthesized on the basis of the cDNA base sequence described in any of Sequence Nos. 11 to 21, 23, 25, 27, 29, 31, 33, 35, 37 and 39.

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In general, the polymorphism due to the individual difference is frequently observed in human genes. Accordingly, any cDNA that is subjected to insertion or deletion of one or plural nucleotides and/or substitution with other nucleotides in Sequence Nos. 11 to 21, 23, 25, 27, 29, 31, 33, 35, 37 and 39 shall come within the scope of the present invention.

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In a similar manner, any protein that is formed by these modifications comprising insertion or deletion of one or plural amino acids and/or substitution with other amino acids shall come within the scope of the present invention, as far as the protein possesses the activity of any protein having the amino acid sequences represented by Sequence Nos. 1 to 10.

The cDNAs of the present invention include cDNA fragments (more than 10 bp) containing any partial base sequence in the base sequences represented by Sequence Nos. 11 to 20 or in the base sequences represented by Sequence Nos. 21, 23, 25, 27, 29, 31, 33, 35, 37 and 39. Also, DNA fragments consisting of a sense chain and an anti-sense chain shall come within this scope. These DNA fragments can be utilized as the probes for the gene diagnosis.

In addition to the activities and uses described above, the polynucleotides and proteins of the present invention may exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a

particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the

corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands.

5 Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved
10 in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for
15 commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor
20 Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

25 Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In
30 such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation,

such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular

Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

5 Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and
10 Measurement of mouse and human Interferon γ , Schreiber, R.D. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

15 Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12,
20 John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6-Nordan, R. In Current Protocols in
25 Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In Current Protocols in Immunology.
30 J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C.

and Turner, K.J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

5 Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immunol. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

20 A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or

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other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitus, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-

specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by

immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate

disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from

the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan,

A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans);
5 Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl.
10 Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowman et al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al.,
15 Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses
20 and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J.J. and Brunswick, M. In Current Protocols in Immunology. J.E.e.a. Coligan eds.
25 Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without
30 limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro

assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

5 Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559,
10 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of
15 Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

 Assays for lymphocyte survival/apoptosis (which will
20 identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca
25 et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

30 Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood

84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

5 A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates
10 involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with
15 irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with
20 chemotherapy to prevent or treat consequent myelosuppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use
25 in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell
30 disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well

as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc.,

New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of

bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be

useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or

regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin- β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those

described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or

inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their
5 ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of
10 cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of
15 receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include
20 without limitation those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions
25 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670,
30 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by

inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth

5 Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example,

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psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

Examples

The present invention is embodied in more detail by the following examples, but this embodiment is not intended to restrict the present invention. The basic operations and the enzyme reactions with regard to the DNA recombination are carried out according to the literature ["Molecular Cloning. A Laboratory Manual", Cold Spring Harbor Laboratory, 1989]. Unless otherwise stated, restrictive enzymes and a variety of modification enzymes to be used were those available from TAKARA SHUZO. The manufacturer's instructions were used for the buffer compositions as well as for the reaction conditions, in each of the enzyme reactions. The cDNA synthesis was carried out according to the literature [Kato, S. et al., Gene 150: 243-250 (1994)].

(1) Selection of cDNAs Encoding Proteins Having Hydrophobic Domains

cDNA libraries (WO97/33993) of osteosarcoma cell line Saos-2 and cDNA libraries (WO97/15596) of tissues of stomach cancer delivered by the operation were used for the cDNA libraries. Full-length cDNA clones were selected from respective libraries and the whole base sequences thereof were determined to construct a homo/protein cDNA bank consisting of the full-length cDNA clones. The

hydrophobicity/hydrophilicity profiles were obtained for proteins encoded by the full-length cDNA clones registered in the homo/protein cDNA bank by the Kyte-Doolittle method [Kyte, J. & Doolittle, R. F., J. Mol. Biol. 157: 105-132 (1982)] to examine the presence or absence of a hydrophobic region. Any clone that has a hydrophobic region being putative as a secretory signal or a transmembrane domain in the amino acid sequence of an encoded protein was selected as a clone candidate.

(2) Protein Synthesis by In Vitro Translation

The plasmid vector bearing the cDNA of the present invention was used for in vitro transcription/translation with a T_NT rabbit reticulocyte lysate kit (Promega). In this case, [³⁵S]methionine was added to label the expression product with a radioisotope. Each of the reactions was carried out according to the protocols attached to the kit. Two micrograms of the plasmid was reacted at 30°C for 90 minutes in a total 25 µl volume of the reaction solution containing 12.5 µl of T_NT rabbit reticulocyte lysate, 0.5 µl of a buffer solution (attached to kit), 2 µl of an amino acid mixture (methionine-free), 2 µl of [³⁵S]methionine (Amersham) (0.37 MBq/µl), 0.5 µl of T7RNA polymerase, and 20 U of RNasin. Also, an experiment in the presence of a membrane system was carried out by adding to this reaction system 2.5 µl of a canine pancreas microsome fraction (Promega). To 3 µl of the resulting reaction solution was added 2 µl of the SDS sampling buffer (125 mM Tris-hydrochloric acid buffer, pH 6.8, 120 mM 2-mercaptoethanol, 2% SDS solution, 0.025% bromophenol blue, and 20% glycerol) and the resulting mixture was heated at 95°C for 3 minutes and then subjected to SDS-polyacrylamide gel electrophoresis. The molecular weight

of the translation product was determined by carrying out the autoradiography.

(3) Expression by COS7

Escherichia coli bearing the expression vector of the protein of the present invention was incubated at 37°C for 2 hours in 2 ml of the 2xYT culture medium containing 100 µg/ml of ampicillin, the helper phage M13K07 (50 µl) was added, and the incubation was continued at 37°C overnight. A supernatant separated by centrifugation underwent precipitation with polyethylene glycol to obtain single-stranded phage particles. These particles were suspended in 100 µl of 1 mM Tris-0.1 mM EDTA, pH 8 (TE).

The culture cells originating from the simian kidney, COS7, were incubated at 37°C in the presence of 5% CO₂ in the Dulbecco's modified Eagle's culture medium (DMEM) containing 10% fetal calf albumin. Into a 6-well plate (Nunc Inc., 3 cm in the well diameter) were inoculated 1 × 10⁵ COS7 cells and incubation was carried out at 37°C for 22 hours in the presence of 5% CO₂. After the culture medium was removed, the cell surface was washed with a phosphate buffer solution and then washed again with DMEM containing 50 mM Tris-hydrochloric acid (pH 7.5) (TDMEM). To the resulting cells was added a suspension of 1 µl of the single-stranded phage suspension, 0.6 ml of the DMEM culture medium, and 3 µl of TRANSFECTAM™ (IBF Inc.) and the resulting mixture was incubated at 37°C for 3 hours in the presence of 5% CO₂. After the sample solution was removed, the cell surface was washed with TDMEM, 2 ml per well of DMEM containing 10% fetal calf albumin was added, and the incubation was carried out at 37°C for 2 days in the presence of 5% CO₂. After the culture medium was replaced by a culture medium containing [³⁵S]cystine or

[³⁵S]methionine, the incubation was carried out for one hour. After the culture medium and the cells were separated by centrifugation, proteins in the culture fraction and the cell-membrane fraction were subjected to SDS-PAGE.

(4) Clone Examples

<HP00631> (Sequence Nos. 1, 11, and 21)

Determination of the whole base sequence of the cDNA insert of clone HP00631 obtained from cDNA libraries of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 25-bp 5'-nontranslation region, a 717-bp ORF, and a 343-bp 3'-nontranslation region. The ORF codes for a protein consisting of 238 amino acid residues and there existed five putative transmembrane domains. Figure 1 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of a high molecular weight. When expressed in COS7 cells, an expression product of about 25 kDa was observed in the membrane fraction.

The search of the protein data base by using the amino acid sequence of the present protein revealed that the protein was analogous to the golden hamster androgen-regulated protein FAR-17 (PIR Accession No. A54313). Table 2 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the golden hamster androgen-regulated protein FAR-17 (GH). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 38.0% in the entire

region.

Table 2

5	HP M-----ALVPCQVLRMAILLSYCSILCNKYKAIEMPSHQTYGGSWKFLTFIDLVIQAVFFG
	* * * * * * * * * * * * * * *
	GH MTRTTTCVYHFLVWNWYIFLNY-YIPLIGKDEKLKEFHDGGRSKYLTLLNLLLQAIFFG
	HP ICVLTDLSSLLTRGSGNQEQERQLKKLI-SLRDWMLAVLAFPVGVFVAVFWIIYAYDRE
	* * * * * * * * * * * * * * * * * * * * *
10	GH VACLDD---VLKRIIG-----RKDIKFITSTRDLLFSTLVFPISTFIFLVFWTLFYDRES
	HP MIYPKLLDNFIPGWLNHGMHTTVLPFILIEMRTSHHQYPSRSSGLTAICTFSVGYILWVC
	**** * * * * * * * * * * * * * * * * *
	GH LIYPKGLDDYFPAWLNHAMHTYILLFVLVETILRPHHYPSKKLGLALLGACNLAYITRVL
	HP WVHVVTGMWVYPFLEHIGPGARIIFFGSTTILMNFLYLLGEVLNNYIW-DTQKSMEEEKE
15	* * * * * * * * * * * * * * * * * * * * *
	GH WRYSQTGNWVYPVFASLNPLGIIIFFLVCYILNASIYLVGEKINHVKWGATVK---PLMK
	HP KPKLE
	* *
	GH KKK---

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. R22829) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP02403> (Sequence Nos. 2, 12, and 23)

30 Determination of the whole base sequence of the cDNA insert of clone HP02403 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 6-bp 5'-nontranslation region, a 585-bp ORF, and a 577-

bp 3'-nontranslation region. The ORF codes for a protein consisting of 194 amino acid residues and there existed one putative transmembrane domain at the C-terminus. Figure 2 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 22 kDa that was almost identical with the molecular weight of 21,959 predicted from the ORF. When expressed in COS7 cells, an expression product of about 21 kDa was observed in the membrane fraction.

The search of the protein data base by using the amino acid sequence of the present protein revealed that the protein was analogous to the Japanese quail apoptosis regulator NR-13 (SWISS-PROT Accession No. Q90343). Table 3 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the Japanese quail apoptosis regulator NR-13 (CC). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 31.5% in the entire region.

Table 3

	HP	MADPLRERTELLADYLGYCAREPGTPEPAPSTPEAAVLRSAARLRQIHRSFF--SAYL
		* * * * * * * * * * * * * * * * * *
5	CC	MPGSLKEETALLLEDYFQHRA---GGAALPPS-ATAAELRRAAELERRERPFRRSCAPL
	HP	GYPGNRFELVAL--MADSVLSDSPGPTWGRVVTLVTFAGTLLERGPLVTARWKKWGFQPR
		* * * * * * * * * * * * * * * * *
	CC	ARAEPR-EAAALLRKVAAQLETDGGLNWGRLLALVVFAGTL-----A
	HP	LKEQEGDVARDQCQRLVALLSSRLMGQHRAWLQAQGGWDGFCHEFF-RTPPFPLAFWRKQLVQ
10		* * * * * * * * * * * * * * * * *
	CC	AALAESACEEGPSRLAAALTAYLAEEQGEWMEEHGGWDGFCRFFGRHGSQPADQNSTLSN
	HP	A-FLSCLLTAFIYLWTRLL
		* * * * * * * * * * * * * * * * *
	CC	AIMAAAGFGIAGLAFLLVVR

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. AA098865) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP02420> (Sequence Nos. 3, 13, and 25)

Determination of the whole base sequence of the cDNA insert of clone HP02420 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 35-bp 5'-nontranslation region, a 420-bp ORF, and a 169-bp 3'-nontranslation region. The ORF codes for a protein consisting of 139 amino acid residues and there existed three putative transmembrane domains. Figure 3 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. AA044799) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

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<HP10349> (Sequence Nos. 4, 14, and 27)

Determination of the whole base sequence of the cDNA insert of clone HP10349 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 16-bp 5'-nontranslation region, a 972-bp ORF, and a 133-bp 3'-nontranslation region. The ORF codes for a protein consisting of 323 amino acid residues and there existed a secretory signal at the N-terminus and one putative transmembrane domain at the C-terminus. Figure 4 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 36 kDa that was almost identical with the molecular weight of 36,200 predicted from the ORF.

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. F13066) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

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<HP10508> (Sequence Nos. 5, 15, and 29)

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Determination of the whole base sequence of the cDNA insert of clone HP10508 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of

a 33-bp 5'-nontranslation region, a 696-bp ORF, and a 98-bp 3'-nontranslation region. The ORF codes for a protein consisting of 231 amino acid residues and there existed four transmembrane domains. Figure 5 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of a high molecular weight. When expressed in C07 cells, an expression product of about 22 kDa was observed in the supernatant fraction and the membrane fraction.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. AA484181) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10524> (Sequence Nos. 6, 16, and 31)

Determination of the whole base sequence of the cDNA insert of clone HP10524 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 308-bp 5'-nontranslation region, a 294-bp ORF, and a 587-bp 3'-nontranslation region. The ORF codes for a protein consisting of 97 amino acid residues and possessed one transmembrane domain. Figure 6 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 21 kDa that was larger than the molecular weight of 10,673 predicted from the ORF. When expressed in COS cells, an expression product of about 26 kDa was observed in the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein has revealed that the protein was analogous to the human glycoporphin C (SWISS-PROT Accession No. P04921). Table 5 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the human glycoporphin C (GP). Therein, the marks of - and * represent a gap and an amino acid residue identical with the protein of the present invention, respectively. The both proteins possessed a homology of 30.5% in the entire region.

Table 5

HP	M-----TSLLTTP---SPREELMTTPILQPTALS-PEDG---AST-----A
15	* ** * * ** * * * ** **
GP	MWSTRSPNSTAWPLSLEPDPGMASASTTMHTTTIAEPDPGMSGWPDGRMETSTPTIMDIV
HP	LIAVVITVVFLTLLSVVILIFFYLYKNKGSYVTYE--PTEGEPSAIVQMESD----LAKG
	** ** * * * * * * * * * * ** ** * *
GP	VIAGVIAAVAIVLVSLLFVMLRYMYRHKGTYHTNEAKGTEFAESADAALQGDPAEQDAGD
20	HP SEKEEYFI
	* ****
GP	SSRKEYFI

25 Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. R21992) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

30 <HP10529> (Sequence Nos. 7, 17, and 33)

Determination of the whole base sequence of the cDNA insert of clone HP10529 obtained from cDNA libraries of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 93-bp 5'-nontranslation region, a 597-bp ORF, and an 810-bp 3'-nontranslation region. The ORF codes for a protein consisting of 198 amino acid residues and possessed two transmembrane domains. Figure 7 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

The search of the protein data base using the amino acid sequence of the present protein has revealed that the protein was analogous to the *fugu rubripes* putative protein 2 (GenBank Accession No. AF026198). Table 6 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the *fugu rubripes* putative protein 2 (FR). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 56.1% in the entire region.

Table 6

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HP MATLWGGILLRLGSLLSLSCLAL-SVLLLAQLS-DAAKNFEDVRCKICPPYKENSCHIYN
      .* *. ** ..... **.*.*****.. *****
5  FR      MPSDREGLWMLAAFALMTLFLLDNVGVTQAKSFDDVRCKICPPYRNISCHIYN
HP KNISQKDCDCLHVVEPMPVVRGPDVEAYCLRCECKYEERSSVTIKVTIIIIYLSILGLLLLY
      ..*****.*****.*****.* ***** *****.. **.******..* ****
FR RNFTQKDCNCLHVVDPMFVPGNDVEAYCLLCECKYEERSTNTIRVTIIIFLSVVGALLLY
HP MVYLTIVEPILKRRLFGHAQLIQSDDDIGDHQPFANAHDVLARSRSRANVLNKVEYAQQR
10      *** **.*..... ** .....* .* **      .. . . .***** ****
FR MLFLLLVDPILIRKPD-PLAQTLLHNEEDEDIQP-----QMSGDPARGNTVLERVEGAQQR
HP WKLQVQEQRKSVFDRHVLS
      ** *****.***** .*
FR WKKQVQEQRKTVFDRHKML

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. N33899) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10537> (Sequence Nos. 8, 18, and 35)

25 Determination of the whole base sequence of the cDNA insert of clone HP10537 obtained from cDNA libraries of the human osteosarcoma cell line Saos-2 revealed the structure consisting of a 94-bp 5'-nontranslation region, a 423-bp ORF, and a 289-bp 3'-nontranslation region. The

30 ORF codes for a protein consisting of 140 amino acid residues and possessed four putative transmembrane domains. Figure 8 depicts the hydrophobicity/hydrophilicity profile,

obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of a high molecular weight. When expressed in COS cells, an expression product of about 14 kDa was observed in the membrane fraction.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. R36207) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10549> (Sequence Nos. 9, 19, and 37)

Determination of the whole base sequence of the cDNA insert of clone HP10549 obtained from cDNA libraries of the human stomach cancer revealed the structure consisting of an 11-bp 5'-nontranslation region, a 606-bp ORF, and a 1101-bp 3'-nontranslation region. The ORF codes for a protein consisting of 201 amino acid residues and possessed three putative transmembrane domains. Figure 9 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 31 kDa that was larger than the molecular weight of 23,346 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. N28687) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10551> (Sequence Nos. 10, 20, and 39)

Determination of the whole base sequence of the cDNA insert of clone HP10551 obtained from cDNA libraries of the human stomach cancer revealed the structure consisting of a 152-bp 5'-nontranslation region, a 750-bp ORF, and a 93-bp 3'-nontranslation region. The ORF codes for a protein consisting of 249 amino acid residues and possessed four putative transmembrane domains. Figure 10 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of a high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein has revealed that the protein was analogous to the nematode imaginary protein T15B7 (GenBank Accession No. F022985). Table 7 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the nematode imaginary protein T15B7 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 41.3% in the entire region.

Table 7

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HP MASDEDGTNGGASEAGEDREAPGKRRRLGFLATAWLFYDIAMTAGLVLAIAMVRFYM
                                     ..* . * . . ** . . . *
5  SC                               MSVQTYLVAYNVLQILGWSAILVKTVLGLA
HP EKGTHRGLYKSIQKTLKFFQTFALLEIVHCLIGIVPTSVIVTGQVSSRIFMWVLITHSI
.  * . **.* . ***.*** *.*.* .*.***.*** .** * *
SC  NGLTWPQLYESVEFELKIFQTAAILEVIHAIVGLVRSPVGTAMQVTSRVVLVWPILHLC
HP KPIQNEESVVLFLVAWTVTEITRYSFYTFSLLDH-LPYFIKWARYNEFFIILYPVGVAGEL
10 .. . . * *.****.***.*****.***.***.***.***.***.***.***.***
SC STARFSIGVPLLLVAWSVTEVIRYSFYALSVLKQPIPYFLLYLRYTLFYVLYPMGVSGEL
HP LTIYAALPHVKKTGMFSIRLPNKYNVSFDYYYFILLITMASYIPLEFPQLYFHMLRQRRKVL
***.*.* .*. . . . .***. * . . . . *.*. **** *****.*. ***.*.*
SC LTLFASLNEVDEKKILTLEMPNRLNMGISFWWWLIIAALSYPGFPQLYFYMIGQRKKIL
15 HP HGEVIVEKDD
      *
SC GGGSKKKOLIATNONSTLFINYSPKTKROWKCFSAEFVDILCSPFGIFVTVIREESWKS

```

20 Furthermore, the search of the GenBank using the base
sequences of the present cDNA has revealed the
registration of sequences that possessed a homology of 90%
or more (for example, Accession No. N67509) in EST, but,
since they are partial sequences, it can not be judged
25 whether or not any of these sequences codes for the same
protein as the protein of the present invention.

INDUSTRIAL APPLICABILITY

30 The present invention provides human proteins having hydrophobic domains, DNAs coding for these proteins, and expression vectors of these DNAs as well as eucaryotic cells expressing these DNAs. All of the proteins of the present invention are secreted or exist in the cell

membrane, so that they are considered to be proteins controlling the proliferation and the differentiation of the cells. Accordingly, the proteins of the present invention can be employed as pharmaceuticals such as carcinostatic agents relating to the control of the proliferation and the differentiation of the cells or as antigens for preparing antibodies against these proteins. The DNAs of the present invention can be utilized as probes for the gene diagnosis and gene sources for the gene therapy. Furthermore, the DNAs can be utilized for large-scale expression of these proteins. Cells, wherein these genes are introduced to express these proteins, can be utilized for detection of the corresponding receptors and ligands, screening of novel low-molecular pharmaceuticals, and so on.

The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are derived and may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is

a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

Organisms that have enhanced, reduced, or modified
5 expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene
10 (Albert and Morris, 1994, Trends Pharmacol. Sci. 15(7): 250-254; Lavarosky et al., 1997, Biochem. Mol. Med. 62(1): 11-22; and Hampel, 1998, Prog. Nucleic Acid Res. Mol. Biol. 58: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of
15 the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic
20 control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s)
25 corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene
30 inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, Bioessays 14(9): 629-633; Zwaal

et al., 1993, Proc. Natl. Acad. Sci. USA 90(16): 7431-7435; Clark et al., 1994, Proc. Natl. Acad. Sci. USA 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably
5 detected by positive/negative genetic selection strategies (Mansour et al., 1988, Nature 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614,396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with
10 altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of
15 molecules that interact with the protein product(s) of the corresponding gene(s). Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular
20 and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such
25 domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a
30 disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein,

where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide, as determined by those of skill in the art. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous, or related to that encoded by the polynucleotides.

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions,

more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Table

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp) [†]	Hybridization Temperature and Buffer [†]	Wash Temperature and Buffer [†]
A	DNA : DNA	≥50	65°C; 1×SSC -or- 42°C; 1×SSC, 50% formamide	65°C; 0.3×SSC
B	DNA : DNA	<50	T _B *; 1×SSC	T _B *; 1×SSC
C	DNA : RNA	≥50	67°C; 1×SSC -or- 45°C; 1×SSC, 50% formamide	67°C; 0.3×SSC
D	DNA : RNA	<50	T _D *; 1×SSC	T _D *; 1×SSC
E	RNA : RNA	≥50	70°C; 1×SSC -or- 50°C; 1×SSC, 50% formamide	70°C; 0.3×SSC
F	RNA : RNA	<50	T _F *; 1×SSC	T _F *; 1×SSC
G	DNA : DNA	≥50	65°C; 4×SSC -or- 42°C; 4×SSC, 50% formamide	65°C; 1×SSC
H	DNA : DNA	<50	T _H *; 4×SSC	T _H *; 4×SSC
I	DNA : RNA	≥50	67°C; 4×SSC -or- 45°C; 4×SSC, 50% formamide	67°C; 1×SSC
J	DNA : RNA	<50	T _J *; 4×SSC	T _J *; 4×SSC
K	RNA : RNA	≥50	70°C; 4×SSC -or- 50°C; 4×SSC, 50% formamide	67°C; 1×SSC
L	RNA : RNA	<50	T _L *; 2×SSC	T _L *; 2×SSC
M	DNA : DNA	≥50	50°C; 4×SSC -or- 40°C; 6×SSC, 50% formamide	50°C; 2×SSC
N	DNA : DNA	<50	T _N *; 6×SSC	T _N *; 6×SSC
O	DNA : RNA	≥50	55°C; 4×SSC -or- 42°C; 6×SSC, 50% formamide	55°C; 2×SSC
P	DNA : RNA	<50	T _P *; 6×SSC	T _P *; 6×SSC
Q	RNA : RNA	≥50	60°C; 4×SSC -or- 45°C; 6×SSC, 50% formamide	60°C; 2×SSC
R	RNA : RNA	<50	T _R *; 4×SSC	T _R *; 4×SSC

‡ : The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

† : SSPE (1×SSPE is 0.15M NaCl, 10mM NaH₂PO₄, and 1.25mM EDTA, pH7.4) can be substituted for SSC (1×SSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R : The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(°C)=2(#of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(°C)=81.5 + 16.6(log₁₀[Na⁺]) + 0.41 (%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na⁺] is the concentration of sodium ions in the hybridization buffer ([Na⁺] for 1×SSC=0.165M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and Current Protocols in Molecular Biology, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the

hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

CLAIMS

1. A protein comprising any of the amino acid sequences represented by Sequence Nos. 1 to 10.
- 5 2. A DNA coding for the protein according to Claim 1.
3. A cDNA comprising any of the base sequences represented by Sequence Nos. 11 to 20.
- 10 4. The cDNA according to Claim 3 comprising any of the base sequences represented by Sequence Nos. 21, 23, 25, 27, 29, 31, 33, 35, 37 and 39.
5. An expression vector capable of expressing the DNA according to any of Claims 2 to 4 by in vitro translation or in eucaryotic cells.
- 15 6. A transformation eucaryotic cell capable of expressing the DNA according to any of Claims 2 to 4 to produce the protein according to Claim 1.

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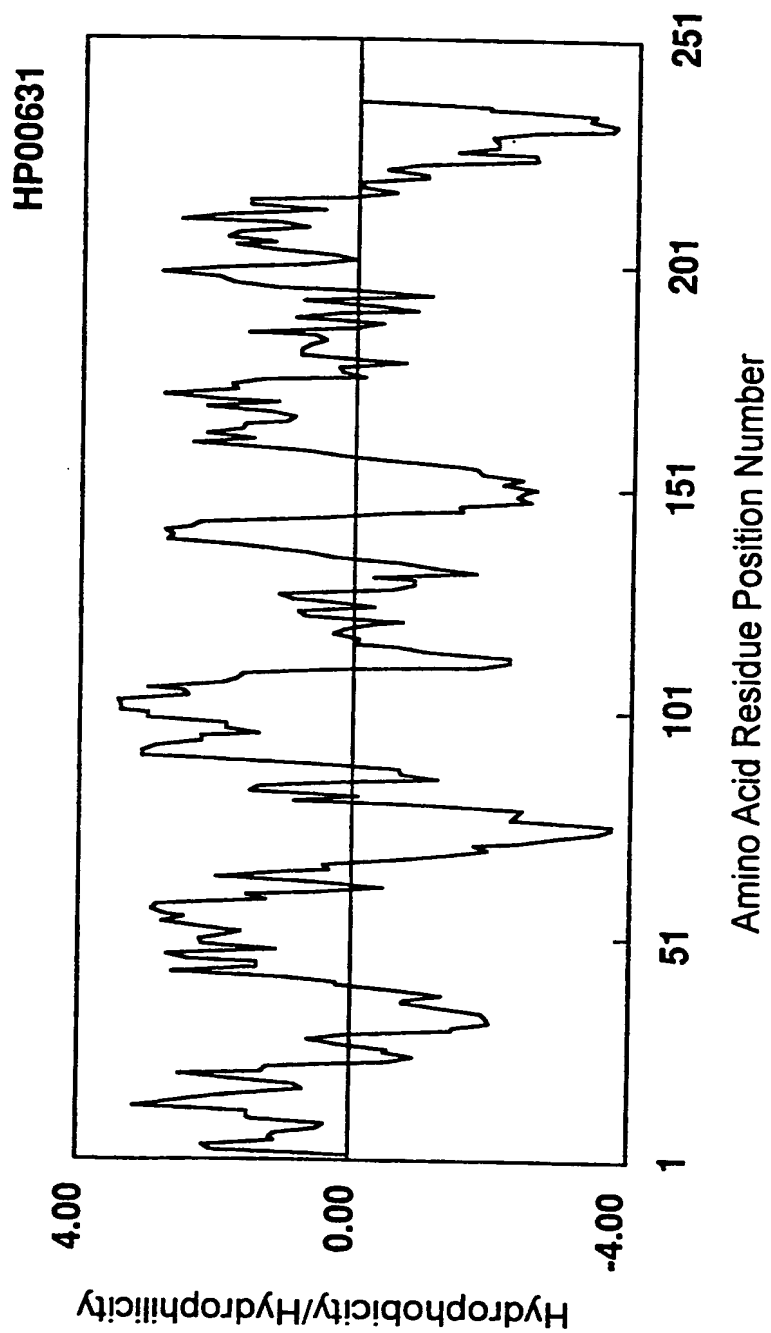


Fig. 1

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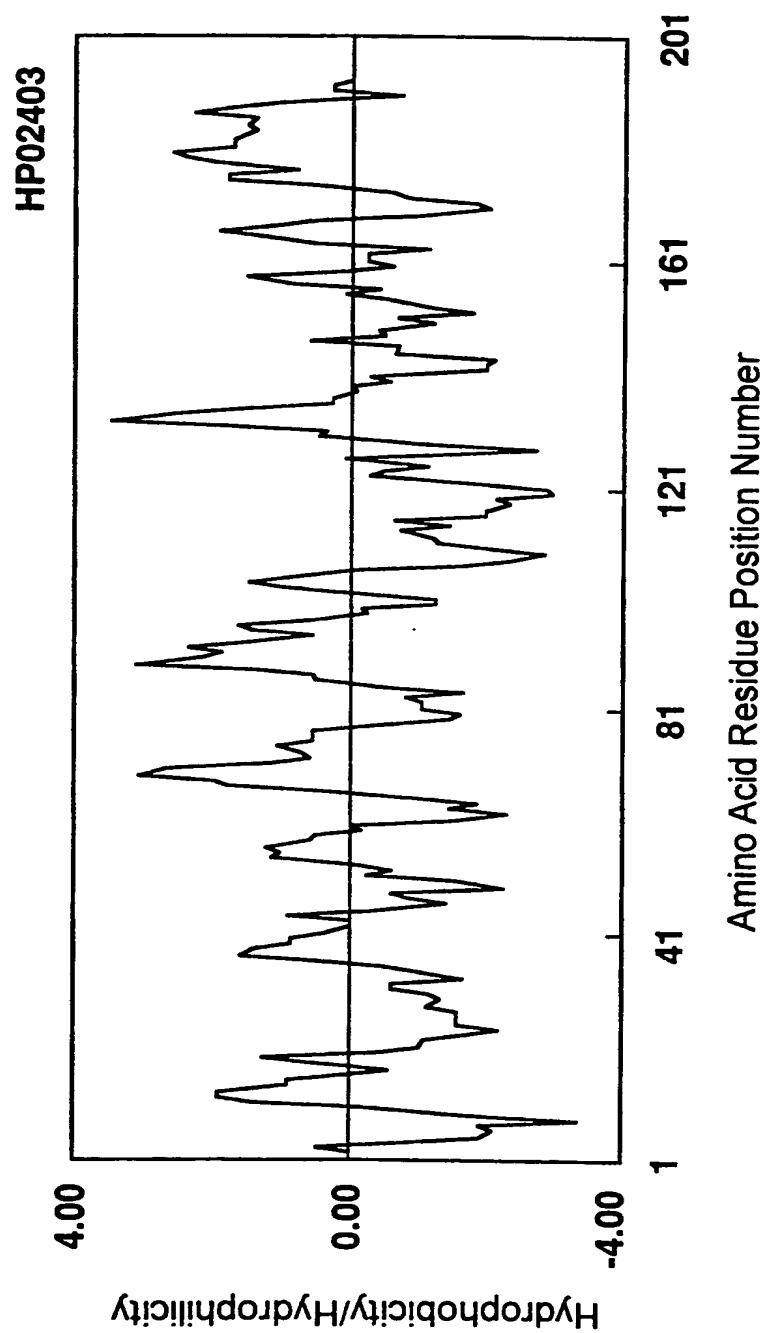


Fig. 2

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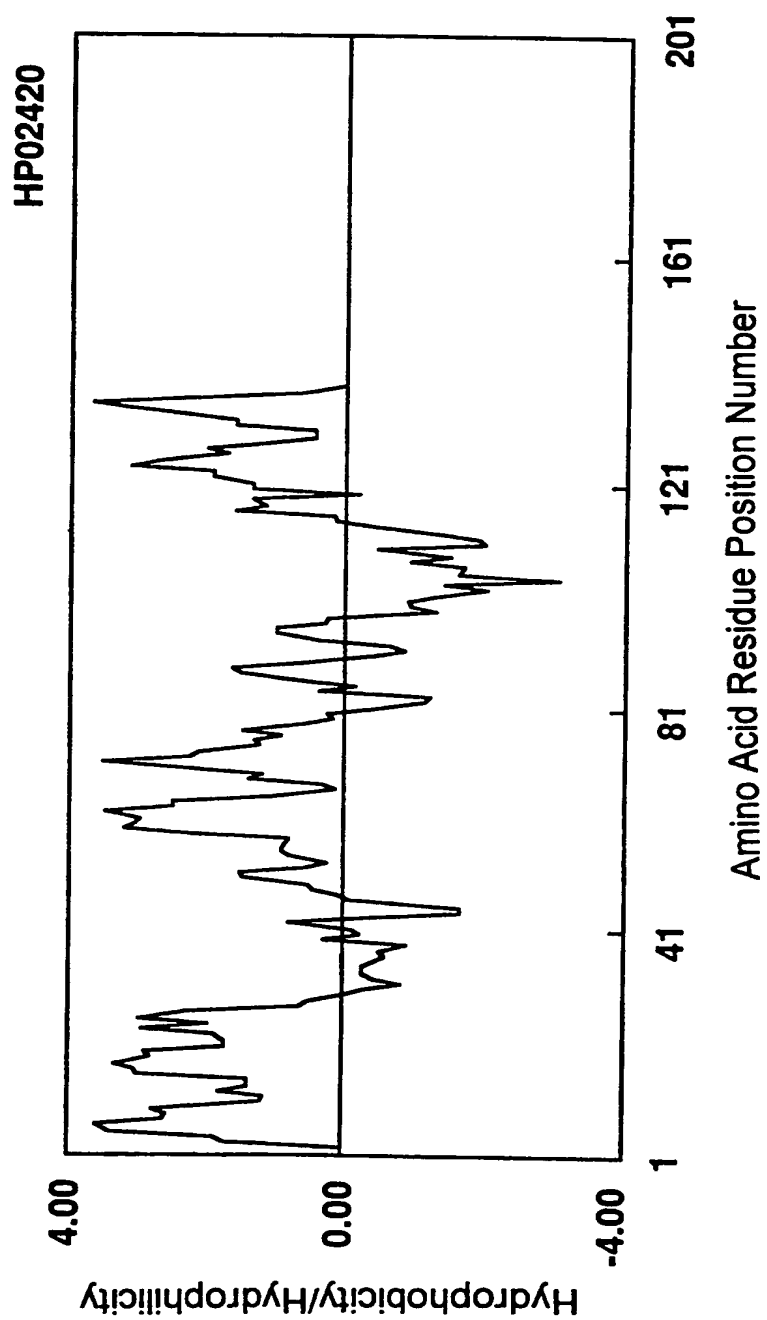


Fig. 3

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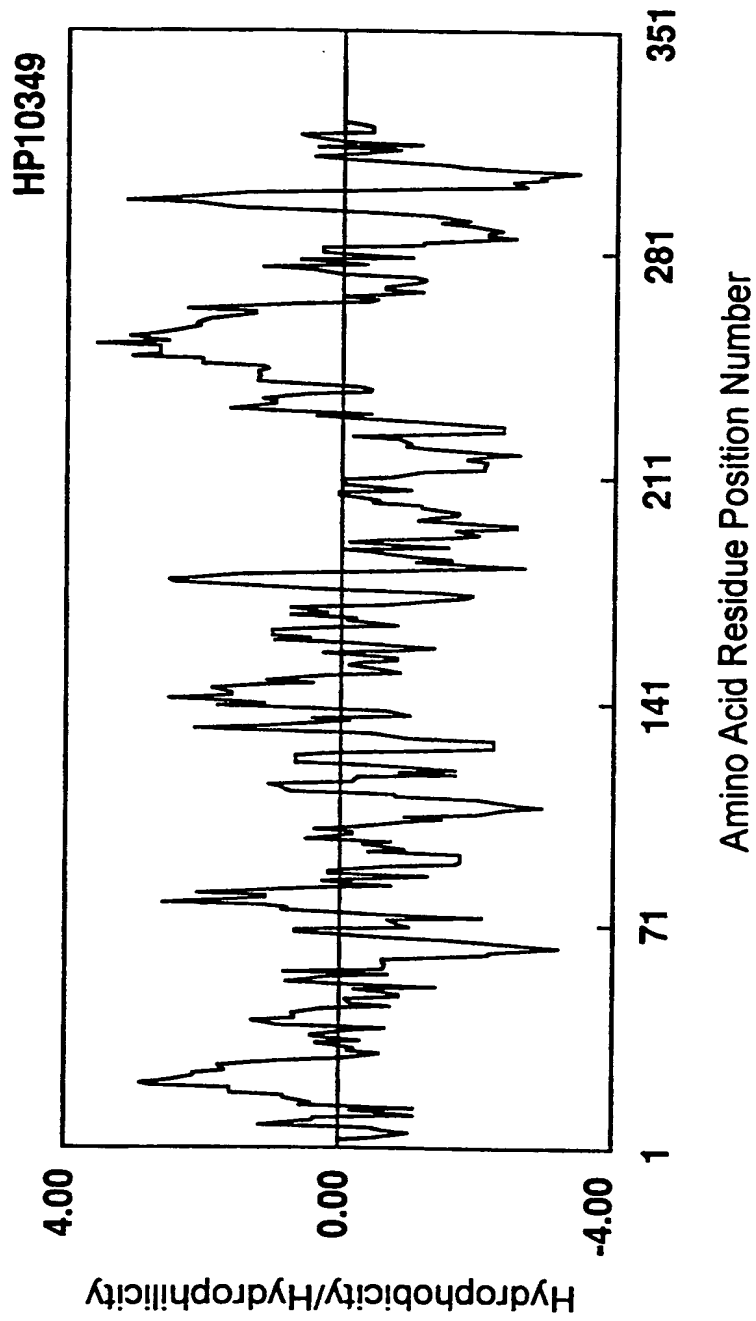


Fig. 4

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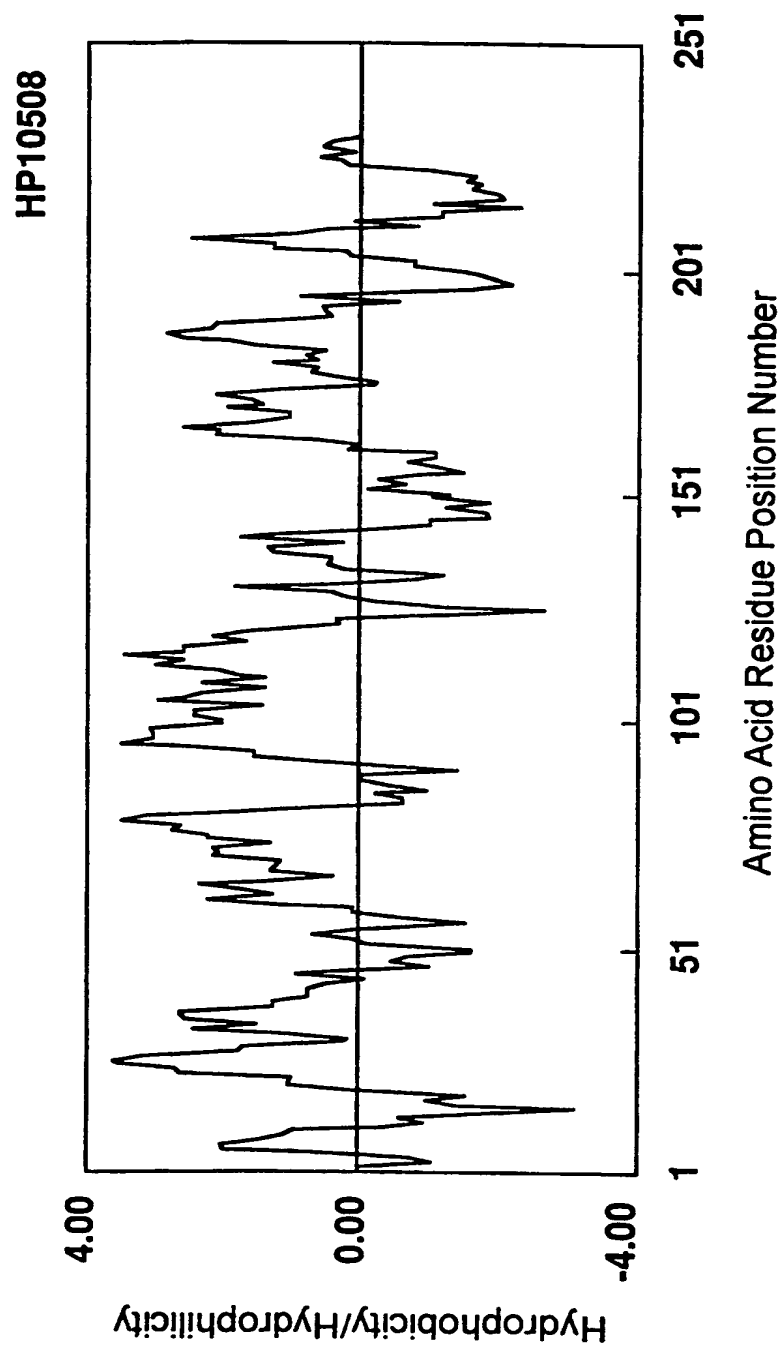


Fig. 5

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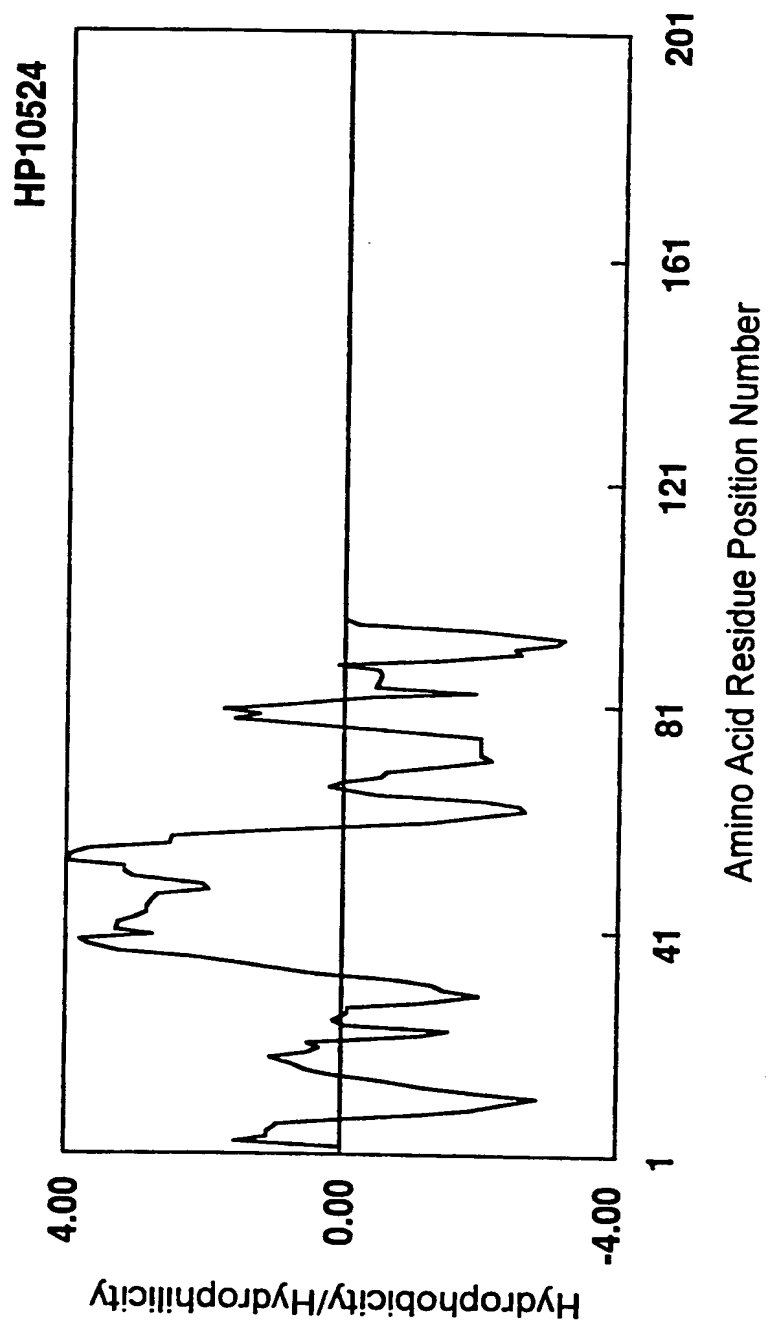


Fig. 6

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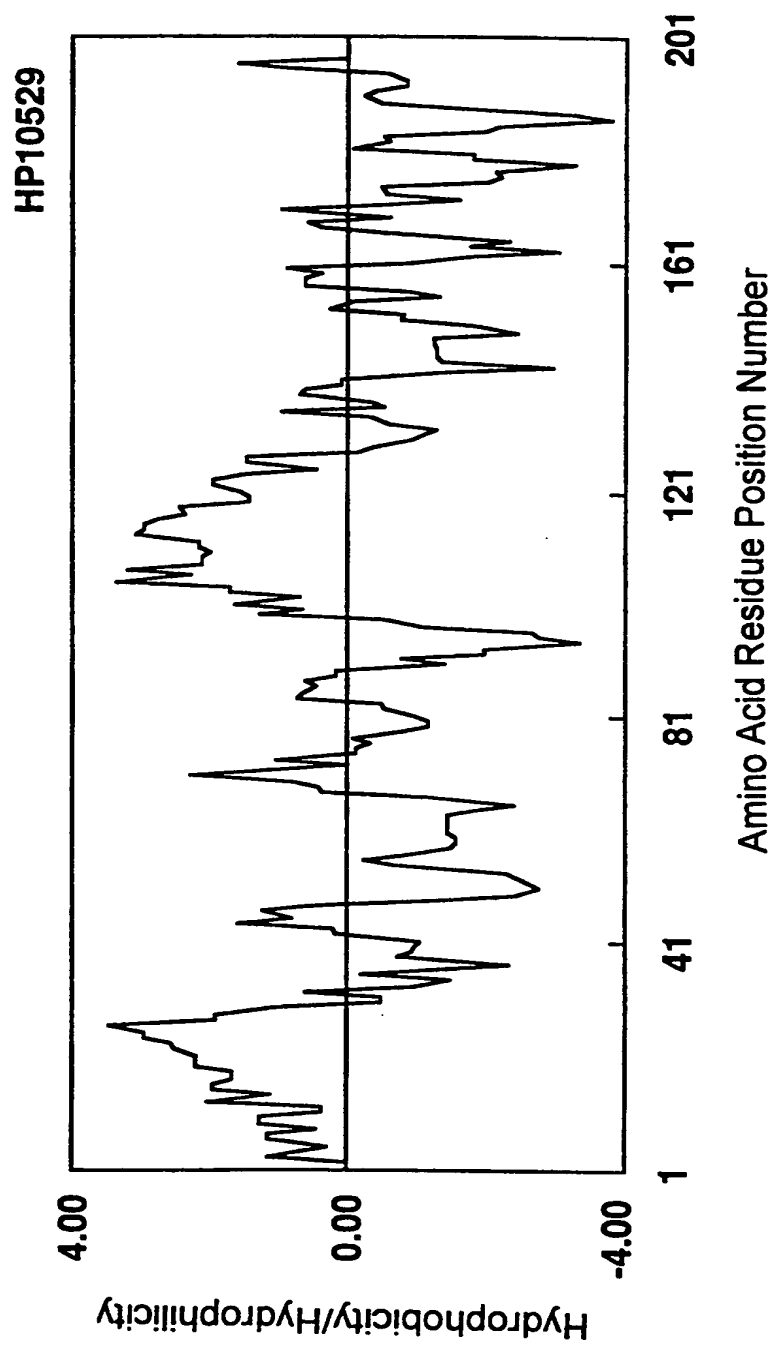


Fig. 7

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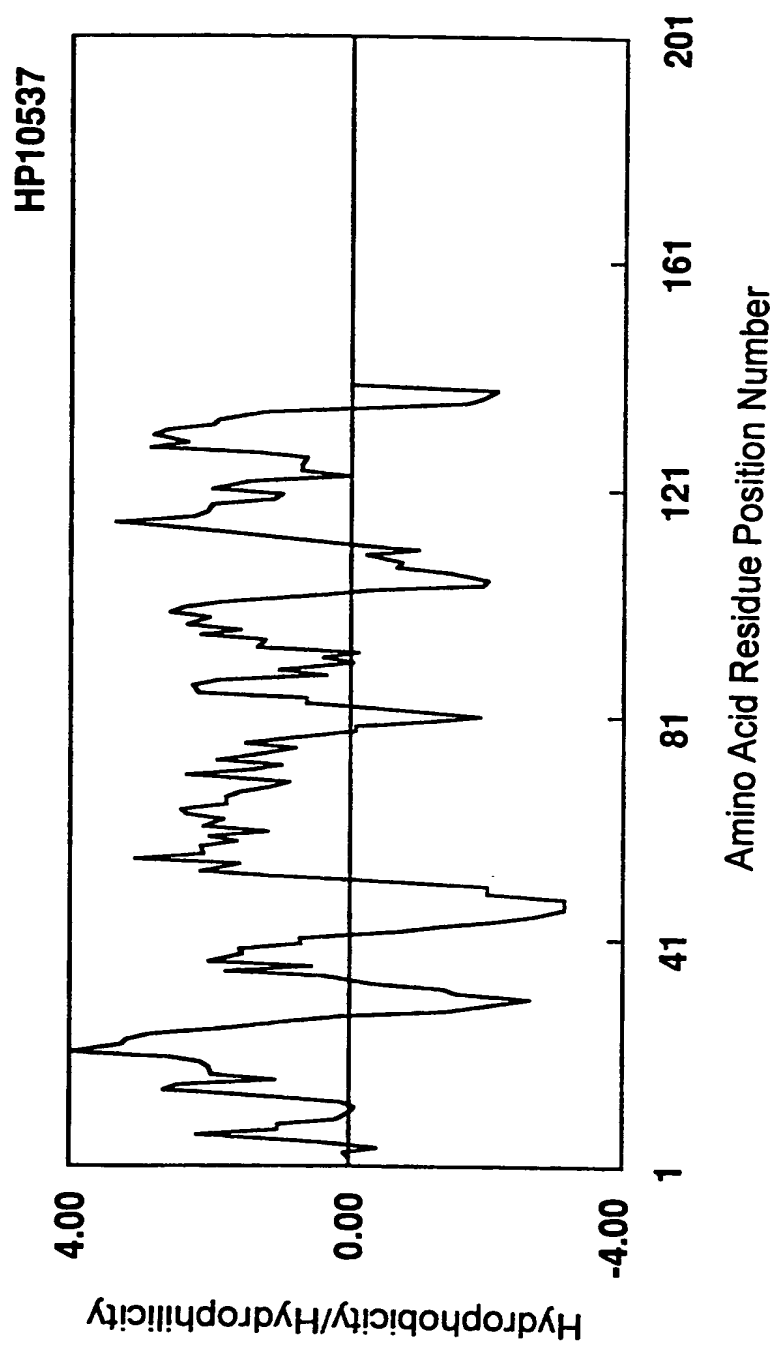


Fig. 8

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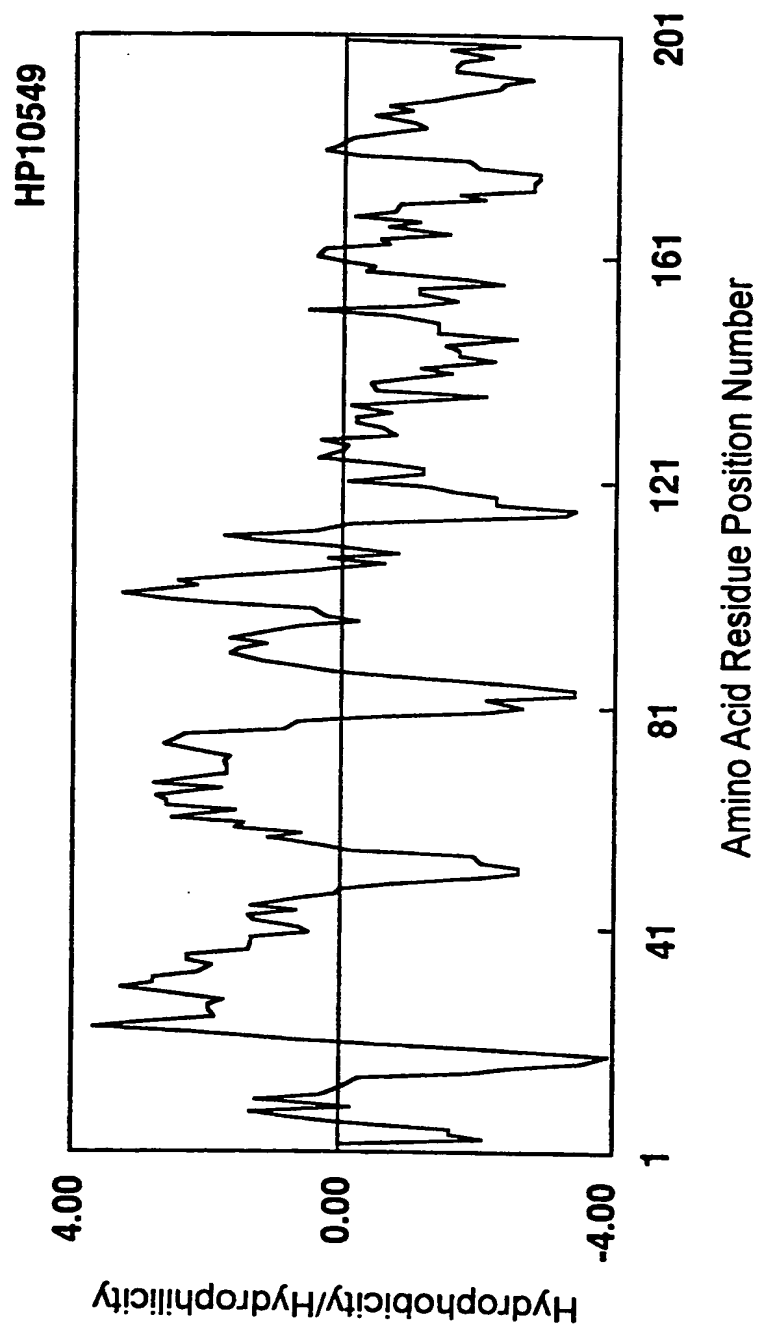


Fig. 9

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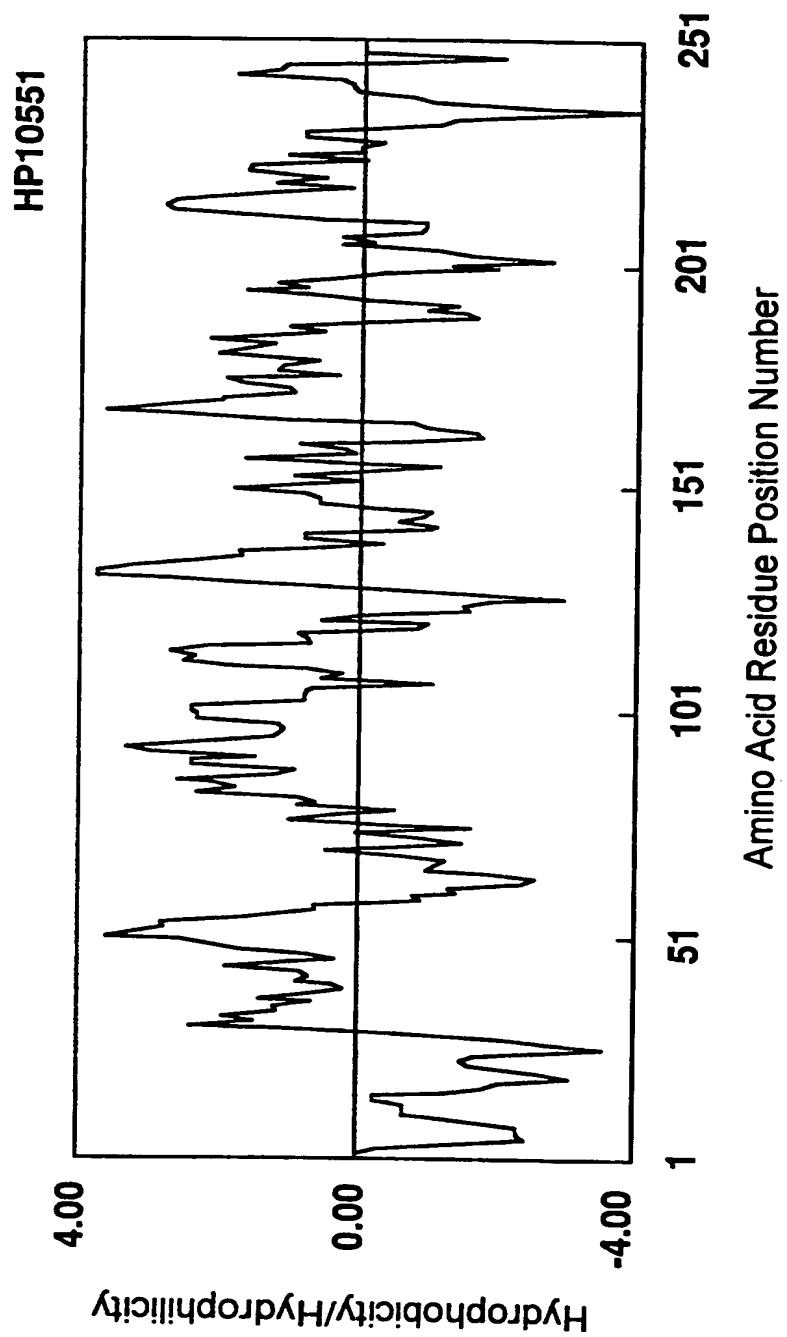


Fig. 10

Sequence listing

<110> Sagami Chemical Research Center et al.

5 <120> Human Proteins Having Hydrophobic Domains And DNAs Encoding These
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 35 40 45

Ile Gln Ala Val Phe Phe Gly Ile Cys Val Leu Thr Asp Leu Ser Ser
 50 55 60

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Leu Leu Thr Arg Gly Ser Gly Asn Gln Glu Gln Glu Arg Gln Leu Lys
 65 70 75 80
 Lys Leu Ile Ser Leu Arg Asp Trp Met Leu Ala Val Leu Ala Phe Pro
 85 90 95
 5 Val Gly Val Phe Val Val Ala Val Phe Trp Ile Ile Tyr Ala Tyr Asp
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 Arg Glu Met Ile Tyr Pro Lys Leu Leu Asp Asn Phe Ile Pro Gly Trp
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 10 130 135 140
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 165 170 175
 15 His His Val Thr Gly Met Trp Val Tyr Pro Phe Leu Glu His Ile Gly
 180 185 190
 Pro Gly Ala Arg Ile Ile Phe Phe Gly Ser Thr Thr Ile Leu Met Asn
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4/45

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50 55 60

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20 100 105 110

Leu Leu Leu Ala Val Ser Leu Thr Val Ala Asn Gly Gly Arg Arg Leu

115 120 125

Ile Ala Asp Cys His Pro Gly Leu Leu Asp Pro Leu Val Pro Leu Asp

130 135 140

25 Glu Gly Pro Gly His Thr Asp Cys Pro Phe Asp Pro Thr Arg Ile Tyr

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 Val Val Leu Phe Leu Val Ala Trp Thr Val Thr Glu Ile Thr Arg Tyr
 130 135 140
 Ser Phe Tyr Thr Phe Ser Leu Leu Asp His Leu Pro Tyr Phe Ile Lys
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 15 Trp Ala Arg Tyr Asn Phe Phe Ile Ile Leu Tyr Pro Val Gly Val Ala
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 Gly Glu Leu Leu Thr Ile Tyr Ala Ala Leu Pro His Val Lys Lys Thr
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 Gly Met Phe Ser Ile Arg Leu Pro Asn Lys Tyr Asn Val Ser Phe Asp
 20 195 200 205
 Tyr Tyr Tyr Phe Leu Leu Ile Thr Met Ala Ser Tyr Ile Pro Leu Phe
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<211> 714

30 <212> DNA

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	gggtctacaa ccatcttaat gaacttctg tacctgctgg gagaagttct gaacaactat	660
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	gagggcgacg tcgcccggga ctgccagcgc ctggtggcct tgctgagctc gcggctcatg	420
	gggcagcacc gcgcctggct gcaggctcag ggcggctggg atggcttttg tcaattcttc	480
	aggaccccct ttccactggc tttttggaga aaacagctgg tcaggctttt tctgtcatgc	540
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13/45

<211> 417

<212> DNA

<213> Homo sapiens

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atacacaatc	gagggcagct	gaagtcacac	atgaaagaag	ccatgatcaa	gcttggtttc	360
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15 <211> 969

<212> DNA

<213> Homo sapiens

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taccctaagg	aagaggagtt	gtacgcagt	cagagaggtt	gcaggctgtt	ttcaatttgt	240
cagtttgtgg	atgatggaat	tgacttaa	cgaactaa	tggaatgtga	atctgcatgt	300
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ctgccattcg	ctgaactgag	acaagaacaa	cttatgtccc	tgatgccaaa	aatgcaccta	420
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30 gaatcatctc	taagcaaaat	gtcctatctg	caaagagaaa	attcacaagc	gcacaggaat	660
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	gagtttatga atgaacaaaa gctaaacaga tatccagctt cttctcttgt ggttgtaga	900
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	ggcacctgctc tggggcacgt ggccaatccc cggggcgtg tcacgccgga gtacacctga	180
15	gccaatgtca tctctgtcgg ctgggggctg ctgagcggtt ccgtgggact tgtggccctc	240
	ctggcgtcca ggaaccttct tcgccctcca ctgcaactgg tcctgctggc actagctctg	300
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15/45

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 aagaacaaag gcagctacgt cacctatgaa cctacagaag gtgagcccag tgccatcgtc 240
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 agatgtaaat gtatctgccc tccctataaa gaaaattctg ggcatattta taataagaac 180
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 cagagtgatg atgatattgg ggatcaccag ccttttgcaa atgcacacga tgtgctagcc 480
 cgctcccga gtcgagccaa cgtgctgaac aaggtagaat atgcacagca gcgctggaag 540
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<210> 18
 <211> 420
 <212> DNA
 25 <213> Homo sapiens

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 30 ttcacccccg aggagtatga caagcaggac attcagctgg tggccgcgct ctctgtcacc 180
 ctgggcctct ttgcagtgga gctggccggt ttcctctcag gagtctccat gttcaacagc 240
 acccagagcc tcattctccat tggggctcac tgtagtgcac ccgtggccct gtccttcttc 300

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atattcgagc gttgggagtg cactacgtat tggtagattt ttgtcttctg cagtgcctt 360
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<210> 19

5 <211> 603

<212> DNA

<213> Homo sapiens

<400> 19

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ttcaccttct gtggttcctt cacgggctgg aagagacatg gggcccacat ctacctcacg 180
atgtcctctt ccattgccat ctgggtggcc tggatcaccc tgctcatgct tcttgacttt 240
gaccgcaggt gggatgacac catcctcagc tccgccttgg ctgccaatgg ctgggtgttc 300
15 ctgttggett atgttagtcc cgagttttgg ctgtctcaca agcaacgaaa ccccatggat 360
tatcctgttg aggatgcttt ctgtaaacct caactcgtga agaagagcta tgggtgtggag 420
aacagagcct actctcaaga ggaaatcaact caagggtttt aagagacagg ggacacgctc 480
tatgccccct attccacaca ttttcagctg cagaaccagc ctccccaaaa ggaattctcc 540
atcccacggg cccacgcttg gcgagccct taaaaagact atgaagtaaa gaaagagggc 600
20 agc 603

<210> 20

<211> 747

<212> DNA

25 <213> Homo sapiens

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30 gacatcgcca tgaccgcggg gtggttggtt ctagctattg ccatggtacg tttttatatg 180
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acatttgctt tgcttgagat agttcaactgt ttaattggaa ttgtacctac ttctgtgatt 300

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	gtgactgggg tccaagtgag ttcaagaatc tttatggtgt ggctcattac tcacagtata	360
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	atcactcgct attccttcta cacattcagc cttcttgacc acttgccata cttcattaaa	480
	tggggccagat ataatttttt tatcatctta tatcctgttg gagttgctgg tgaacttctt	540
5	acaatatacg ctgccttgcc gcatgtgaag aaaacaggaa tgttttcaat aagacttctt	600
	aacaaataca atgtctcttt tgactactat tattttcttc ttataaccat ggcacatcat	660
	atacctttgt ttccacaact ctattttcat atgttacgtc aaagaagaaa ggtgcttcat	720
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	cgg atg gca atc ctg ctg tct tac tgc tct atc ctg tgt aac tac aag	100
20	Arg Met Ala Ile Leu Leu Ser Tyr Cys Ser Ile Leu Cys Asn Tyr Lys	
	10 15 20 25	
	gcc atc gaa atg ccc tca cac cag acc tac gga ggg agc tgg aaa ttc	148
	Ala Ile Glu Met Pro Ser His Gln Thr Tyr Gly Gly Ser Trp Lys Phe	
	30 35 40	
25	ctg acg ttc att gat ctg gtt atc cag gct gtc ttt ttt ggc atc tgt	196
	Leu Thr Phe Ile Asp Leu Val Ile Gln Ala Val Phe Phe Gly Ile Cys	
	45 50 55	
	gtg ctg act gat ctt tcc agt ctt ctg act cga gga agt ggg aac cag	244
	Val Leu Thr Asp Leu Ser Ser Leu Leu Thr Arg Gly Ser Gly Asn Gln	
30	60 65 70	
	gag caa gag agg cag ctc aag aag ctc atc tct ctc cgg gac tgg atg	292
	Glu Gln Glu Arg Gln Leu Lys Lys Leu Ile Ser Leu Arg Asp Trp Met	

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	75	80	85	
	tta gct gtg ttg gcc ttt cct gtt ggg gtt ttt gtt gta gca gtg ttc			340
	Leu Ala Val Leu Ala Phe Pro Val Gly Val Phe Val Val Ala Val Phe			
	90	95	100	105
5	tgg atc att tat gcc tat gac aga gag atg ata tac ccg aag ctg ctg			388
	Trp Ile Ile Tyr Ala Tyr Asp Arg Glu Met Ile Tyr Pro Lys Leu Leu			
		110	115	120
	gat aat ttt atc cca ggg tgg ctg aat cac gga atg cac acg acg gtt			436
	Asp Asn Phe Ile Pro Gly Trp Leu Asn His Gly Met His Thr Thr Val			
10		125	130	135
	ctg ccc ttt ata tta atc gag atg agg aca tcg cac cat cag tat ccc			484
	Leu Pro Phe Ile Leu Ile Glu Met Arg Thr Ser His His Gln Tyr Pro			
		140	145	150
	agc agg agc agc gga ctt acc gcc ata tgt acc ttc tct gtt ggc tat			532
15	Ser Arg Ser Ser Gly Leu Thr Ala Ile Cys Thr Phe Ser Val Gly Tyr			
		155	160	165
	ata tta tgg gtg tgc tgg gtg cat cat gta act ggc atg tgg gtg tac			580
	Ile Leu Trp Val Cys Trp Val His His Val Thr Gly Met Trp Val Tyr			
		170	175	180
20	cct ttc ctg gaa cac att ggc cca gga gcc aga atc atc ttc ttt ggg			628
	Pro Phe Leu Glu His Ile Gly Pro Gly Ala Arg Ile Ile Phe Phe Gly			
		190	195	200
	tct aca acc atc tta atg aac ttc ctg tac ctg ctg gga gaa gtt ctg			676
	Ser Thr Thr Ile Leu Met Asn Phe Leu Tyr Leu Leu Gly Glu Val Leu			
25		205	210	215
	aac aac tat atc tgg gat aca cag aaa agt atg gaa gaa gag aaa gaa			724
	Asn Asn Tyr Ile Trp Asp Thr Gln Lys Ser Met Glu Glu Glu Lys Glu			
		220	225	230
	aag cct aaa ttg gaa tgagatccaa gtctaaacgc aagagctaga ttgagccgcc a			780
30	Lys Pro Lys Leu Glu			
		235		
	ttgaagactc cttccctcg ggcattggca gtgggggaga aaaggcttca aaggaacttg			840

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<210> 22

<211> 238

<212> PRT

10 <213> Homo sapiens

<400> 22

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 10 15 20 25
 Ala Ile Glu Met Pro Ser His Gln Thr Tyr Gly Gly Ser Trp Lys Phe
 30 35 40
 Leu Thr Phe Ile Asp Leu Val Ile Gln Ala Val Phe Phe Gly Ile Cys
 20 45 50 55
 Val Leu Thr Asp Leu Ser Ser Leu Leu Thr Arg Gly Ser Gly Asn Gln
 60 65 70
 Glu Gln Glu Arg Gln Leu Lys Lys Leu Ile Ser Leu Arg Asp Trp Met
 75 80 85
 25 Leu Ala Val Leu Ala Phe Pro Val Gly Val Phe Val Val Ala Val Phe
 90 95 100 105
 Trp Ile Ile Tyr Ala Tyr Asp Arg Glu Met Ile Tyr Pro Lys Leu Leu
 110 115 120
 Asp Asn Phe Ile Pro Gly Trp Leu Asn His Gly Met His Thr Thr Val
 30 125 130 135
 Leu Pro Phe Ile Leu Ile Glu Met Arg Thr Ser His His Gln Tyr Pro
 140 145 150

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Ser Arg Ser Ser Gly Leu Thr Ala Ile Cys Thr Phe Ser Val Gly Tyr
 155 160 165
 Ile Leu Trp Val Cys Trp Val His His Val Thr Gly Met Trp Val Tyr
 170 175 180 185
 5 Pro Phe Leu Glu His Ile Gly Pro Gly Ala Arg Ile Ile Phe Phe Gly
 190 195 200
 Ser Thr Thr Ile Leu Met Asn Phe Leu Tyr Leu Leu Gly Glu Val Leu
 205 210 215
 Asn Asn Tyr Ile Trp Asp Thr Gln Lys Ser Met Glu Glu Glu Lys Glu
 10 220 225 230
 Lys Pro Lys Leu Glu
 235

 <210> 23
 15 <211> 1168
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 Asp Tyr Leu Gly Tyr Cys Ala Arg Glu Pro Gly Thr Pro Glu Pro Ala
 25 15 20 25 30
 cca tcc acg ccc gag gcc gcc gtg ctg cgc tcc gcg gcc gcc agg tta 144
 Pro Ser Thr Pro Glu Ala Ala Val Leu Arg Ser Ala Ala Ala Arg Leu
 35 40 45
 cgg cag att cac cgg tcc ttt ttc tcc gcc tac ctc ggc tac ccc ggg 192
 30 Arg Gln Ile His Arg Ser Phe Phe Ser Ala Tyr Leu Gly Tyr Pro Gly
 50 55 60
 aac cgc ttc gag ctg gtg gcg ctg atg gcg gat tcc gtg ctc tcc gac 240

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	65 70 75	
	agc ccc ggc ccc acc tgg ggc aga gtg gtg acg ctc gtg acc ttc gca	288
	Ser Pro Gly Pro Thr Trp Gly Arg Val Val Thr Leu Val Thr Phe Ala	
5	80 85 90	
	ggg acg ctg ctg gag aga ggg ccg ctg gtg acc gcc cgg tgg aag aag	336
	Gly Thr Leu Leu Glu Arg Gly Pro Leu Val Thr Ala Arg Trp Lys Lys	
	95 100 105 110	
	tgg ggc ttc cag ccg cgg cta aag gag cag gag ggc gac gtc gcc cgg	384
10	Trp Gly Phe Gln Pro Arg Leu Lys Glu Gln Glu Gly Asp Val Ala Arg	
	115 120 125	
	gac tgc cag cgc ctg gtg gcc ttg ctg agc tcg cgg ctc atg ggg cag	432
	Asp Cys Gln Arg Leu Val Ala Leu Leu Ser Ser Arg Leu Met Gly Gln	
	130 135 140	
15	cac cgc gcc tgg ctg cag gct cag ggc ggc tgg gat ggc ttt tgt cac	480
	His Arg Ala Trp Leu Gln Ala Gln Gly Gly Trp Asp Gly Phe Cys His	
	145 150 155	
	ttc ttc agg acc ccc ttt cca ctg gct ttt tgg aga aaa cag ctg gtc	528
	Phe Phe Arg Thr Pro Phe Pro Leu Ala Phe Trp Arg Lys Gln Leu Val	
20	160 165 170	
	cag gct ttt ctg tca tgc ttg tta aca aca gcc ttc att tat ctc tgg	576
	Gln Ala Phe Leu Ser Cys Leu Leu Thr Thr Ala Phe Ile Tyr Leu Trp	
	175 180 185 190	
	aca cga tta tta tgagttttaa aacttttaac ccgcttctac ctgcccaact gt	630
25	Thr Arg Leu Leu	
	gaccaactaa atgacagatg tgtgagaaca agaactgagg gaaagcacct tccccacccc	690
	cagacgtttt tacctgaatg catacaagga gtcctgaggt ggtgatttg cagtggtttt	750
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30	agaaatgggg agtctagagc ctctttatgc caaagaaccg cagaagaaac tgcattccat	870
	taaatgggaa atacagtgct atttgctaaa acttgataa gaggcggaac ctctcatctc	930
	tccacaactt catgtgctgc tgactaattt taaacatggc cacagctggg gcaaaataat	990

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5 <210> 24
<211> 194
<212> PRT
<213> Homo sapiens

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15 Pro Ser Thr Pro Glu Ala Ala Val Leu Arg Ser Ala Ala Ala Arg Leu
35 40 45
Arg Gln Ile His Arg Ser Phe Phe Ser Ala Tyr Leu Gly Tyr Pro Gly
50 55 60
Asn Arg Phe Glu Leu Val Ala Leu Met Ala Asp Ser Val Leu Ser Asp
20 65 70 75
Ser Pro Gly Pro Thr Trp Gly Arg Val Val Thr Leu Val Thr Phe Ala
80 85 90
Gly Thr Leu Leu Glu Arg Gly Pro Leu Val Thr Ala Arg Trp Lys Lys
95 100 105 110
25 Trp Gly Phe Gln Pro Arg Leu Lys Glu Gln Glu Gly Asp Val Ala Arg
115 120 125
Asp Cys Gln Arg Leu Val Ala Leu Leu Ser Ser Arg Leu Met Gly Gln
130 135 140
His Arg Ala Trp Leu Gln Ala Gln Gly Gly Trp Asp Gly Phe Cys His
30 145 150 155
Phe Phe Arg Thr Pro Phe Pro Leu Ala Phe Trp Arg Lys Gln Leu Val
160 165 170

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Gln Ala Phe Leu Ser Cys Leu Leu Thr Thr Ala Phe Ile Tyr Leu Trp
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5 <210> 25
 <211> 624
 <212> DNA
 <213> Homo sapiens

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 15 Val Phe Ser Leu Leu Asp Cys Cys Ala Leu Ile Phe Leu Ser Val Tyr
 10 15 20
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 Phe Ile Ile Thr Leu Ser Asp Leu Glu Cys Asp Tyr Ile Asn Ala Arg
 25 30 35
 20 tca tgt tgc tca aaa tta aac aag tgg gta att cca gaa ttg att ggc 197
 Ser Cys Cys Ser Lys Leu Asn Lys Trp Val Ile Pro Glu Leu Ile Gly
 40 45 50
 cat acc att gtc act gta tta ctg ctc atg tca ttg cac tgg ttc atc 245
 His Thr Ile Val Thr Val Leu Leu Leu Met Ser Leu His Trp Phe Ile
 25 55 60 65 70
 ttc ctt ctc aac tta cct gtt gcc act tgg aat ata tat cga tac att 293
 Phe Leu Leu Asn Leu Pro Val Ala Thr Trp Asn Ile Tyr Arg Tyr Ile
 75 80 85
 atg gtg ccg agt ggt aac atg gga gtg ttt gat cca aca gaa ata cac 341
 30 Met Val Pro Ser Gly Asn Met Gly Val Phe Asp Pro Thr Glu Ile His
 90 95 100
 aat cga ggg cag ctg aag tca cac atg aaa gaa gcc atg atc aag ctt 389

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Asn Arg Gly Gln Leu Lys Ser His Met Lys Glu Ala Met Ile Lys Leu
 105 110 115
 ggt ttc cac ttg ctc tgc ttc ttc atg tat ctt tat agt atg atc tta 437
 Gly Phe His Leu Leu Cys Phe Phe Met Tyr Leu Tyr Ser Met Ile Leu
 5 120 125 130
 gct ttg ata aat gac tgaagctgga gaagccgtgg ttgaagtcag cctacact 490
 Ala Leu Ile Asn Asp
 135
 acagtgcaca gttgaggagc cagagacttc ttaaatacatc cttagaaccg tgaccatagc 550
 10 agtatatatt ttctcttgg aacaaaaaac tattttttgct gtatttttac catataaagt 610
 atttaaaaaa catg 624

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 <211> 139
 15 <212> PRT
 <213> Homo sapiens

 <400> 26

 Met Glu Ala Val Val Phe
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 Val Phe Ser Leu Leu Asp Cys Cys Ala Leu Ile Phe Leu Ser Val Tyr
 10 15 20
 Phe Ile Ile Thr Leu Ser Asp Leu Glu Cys Asp Tyr Ile Asn Ala Arg
 25 30 35
 25 Ser Cys Cys Ser Lys Leu Asn Lys Trp Val Ile Pro Glu Leu Ile Gly
 40 45 50
 His Thr Ile Val Thr Val Leu Leu Leu Met Ser Leu His Trp Phe Ile
 55 60 65 70
 Phe Leu Leu Asn Leu Pro Val Ala Thr Trp Asn Ile Tyr Arg Tyr Ile
 30 75 80 85
 Met Val Pro Ser Gly Asn Met Gly Val Phe Asp Pro Thr Glu Ile His
 90 95 100

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Asn Arg Gly Gln Leu Lys Ser His Met Lys Glu Ala Met Ile Lys Leu
 105 110 115
 Gly Phe His Leu Leu Cys Phe Phe Met Tyr Leu Tyr Ser Met Ile Leu
 120 125 130
 5 Ala Leu Ile Asn Asp
 135

 <210> 27
 <211> 1121
 10 <212> DNA
 <213> Homo sapiens

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 15 Met Ala Ala Pro Lys Gly Ser Leu Trp Val Arg Thr
 1 5 10
 caa ctg ggg ctc ccg ccg ctg ctg ctg ctg acc atg gcc ttg gcc gga 100
 Gln Leu Gly Leu Pro Pro Leu Leu Leu Leu Thr Met Ala Leu Ala Gly
 15 20 25
 20 ggt tcg ggg acc gct tcg gct gaa gca ttt gac tcg gtc ttg ggt gat 148
 Gly Ser Gly Thr Ala Ser Ala Glu Ala Phe Asp Ser Val Leu Gly Asp
 30 35 40
 acg gcg tct tgc cac cgg gcc tgt cag ttg acc tac ccc ttg cac acc 196
 Thr Ala Ser Cys His Arg Ala Cys Gln Leu Thr Tyr Pro Leu His Thr
 25 45 50 55 60
 tac cct aag gaa gag gag ttg tac gca tgt cag aga ggt tgc agg ctg 244
 Tyr Pro Lys Glu Glu Glu Leu Tyr Ala Cys Gln Arg Gly Cys Arg Leu
 65 70 75
 ttt tca att tgt cag ttt gtg gat gat gga att gac tta aat cga act 292
 30 Phe Ser Ile Cys Gln Phe Val Asp Asp Gly Ile Asp Leu Asn Arg Thr
 80 85 90
 aaa ttg gaa tgt gaa tct gca tgt aca gaa gca tat tcc caa tct gat 340

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	Lys	Leu	Glu	Cys	Glu	Ser	Ala	Cys	Thr	Glu	Ala	Tyr	Ser	Gln	Ser	Asp	
	95							100						105			
	gag	caa	tat	gct	tgc	cat	ctt	ggt	tgc	cag	aat	cag	ctg	cca	ttc	gct	388
	Glu	Gln	Tyr	Ala	Cys	His	Leu	Gly	Cys	Gln	Asn	Gln	Leu	Pro	Phe	Ala	
5	110							115						120			
	gaa	ctg	aga	caa	gaa	caa	ctt	atg	tcc	ctg	atg	cca	aaa	atg	cac	cta	436
	Glu	Leu	Arg	Gln	Glu	Gln	Leu	Met	Ser	Leu	Met	Pro	Lys	Met	His	Leu	
	125							130						135		140	
	ctc	ttt	cct	cta	act	ctg	gtg	agg	tca	ttc	tgg	agt	gac	atg	atg	gac	484
10	Leu	Phe	Pro	Leu	Thr	Leu	Val	Arg	Ser	Phe	Trp	Ser	Asp	Met	Met	Asp	
								145						150		155	
	tcc	gca	cag	agc	ttc	ata	acc	tct	tca	tgg	act	ttt	tat	ctt	caa	gcc	532
	Ser	Ala	Gln	Ser	Phe	Ile	Thr	Ser	Ser	Trp	Thr	Phe	Tyr	Leu	Gln	Ala	
								160						165		170	
15	gat	gac	gga	aaa	ata	gtt	ata	ttc	cag	tct	aag	cca	gaa	atc	cag	tac	580
	Asp	Asp	Gly	Lys	Ile	Val	Ile	Phe	Gln	Ser	Lys	Pro	Glu	Ile	Gln	Tyr	
								175						180		185	
	gca	cca	cat	ttg	gag	cag	gag	cct	aca	aat	ttg	aga	gaa	tca	tct	cta	628
	Ala	Pro	His	Leu	Glu	Gln	Glu	Pro	Thr	Asn	Leu	Arg	Glu	Ser	Ser	Leu	
20	190							195						200			
	agc	aaa	atg	tcc	tat	ctg	caa	atg	aga	aat	tca	caa	gcg	cac	agg	aat	676
	Ser	Lys	Met	Ser	Tyr	Leu	Gln	Met	Arg	Asn	Ser	Gln	Ala	His	Arg	Asn	
	205							210						215		220	
	ttt	ctt	gaa	gat	gga	gaa	agt	gat	ggc	ttt	tta	aga	tgc	ctc	tct	ctt	724
25	Phe	Leu	Glu	Asp	Gly	Glu	Ser	Asp	Gly	Phe	Leu	Arg	Cys	Leu	Ser	Leu	
								225						230		235	
	aac	tct	ggg	tgg	att	tta	act	aca	act	ctt	gtc	ctc	tcg	gtg	atg	gta	772
	Asn	Ser	Gly	Trp	Ile	Leu	Thr	Thr	Thr	Leu	Val	Leu	Ser	Val	Met	Val	
								240						245		250	
30	ttg	ctt	tgg	att	tgt	tgt	gca	act	gtt	gct	aca	gct	gtg	gag	cag	tat	820
	Leu	Leu	Trp	Ile	Cys	Cys	Ala	Thr	Val	Ala	Thr	Ala	Val	Glu	Gln	Tyr	
								255						260		265	

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gtt ccc tct gag aag ctg agt atc tat ggt gac ttg gag ttt atg aat 868
 Val Pro Ser Glu Lys Leu Ser Ile Tyr Gly Asp Leu Glu Phe Met Asn
 270 275 280
 gaa caa aag cta aac aga tat cca gct tct tct ctt gtg gtt gtt aga 916
 5 Glu Gln Lys Leu Asn Arg Tyr Pro Ala Ser Ser Leu Val Val Val Arg
 285 290 295 300
 tct aaa act gaa gat cat gaa gaa gca ggg cct cta cct aca aaa gtg 964
 Ser Lys Thr Glu Asp His Glu Glu Ala Gly Pro Leu Pro Thr Lys Val
 305 310 315
 10 aat ctt gct cat tct gaa att taagcatttt tcttttaaaa gacaa 1010
 Asn Leu Ala His Ser Glu Ile
 320
 gtgtaataga catctaaaat tccactcctc atagagcttt taaaatgggtt tcattggata 1070
 taggccttaa gaaatcacta taaaatgcaa ataaagttac tcaaattctgt g 1121
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 <210> 28
 <211> 323
 <212> PRT
 <213> Homo sapiens
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 1 5 10
 Gln Leu Gly Leu Pro Pro Leu Leu Leu Leu Thr Met Ala Leu Ala Gly
 25 15 20 25
 Gly Ser Gly Thr Ala Ser Ala Glu Ala Phe Asp Ser Val Leu Gly Asp
 30 35 40
 Thr Ala Ser Cys His Arg Ala Cys Gln Leu Thr Tyr Pro Leu His Thr
 45 50 55 60
 30 Tyr Pro Lys Glu Glu Glu Leu Tyr Ala Cys Gln Arg Gly Cys Arg Leu
 65 70 75
 Phe Ser Ile Cys Gln Phe Val Asp Asp Gly Ile Asp Leu Asn Arg Thr

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	80	85	90
	Lys Leu Glu Cys Glu Ser Ala Cys Thr Glu Ala Tyr Ser Gln Ser Asp		
	95	100	105
	Glu Gln Tyr Ala Cys His Leu Gly Cys Gln Asn Gln Leu Pro Phe Ala		
5	110	115	120
	Glu Leu Arg Gln Glu Gln Leu Met Ser Leu Met Pro Lys Met His Leu		
	125	130	135 140
	Leu Phe Pro Leu Thr Leu Val Arg Ser Phe Trp Ser Asp Met Met Asp		
	145	150	155
10	Ser Ala Gln Ser Phe Ile Thr Ser Ser Trp Thr Phe Tyr Leu Gln Ala		
	160	165	170
	Asp Asp Gly Lys Ile Val Ile Phe Gln Ser Lys Pro Glu Ile Gln Tyr		
	175	180	185
	Ala Pro His Leu Glu Gln Glu Pro Thr Asn Leu Arg Glu Ser Ser Leu		
15	190	195	200
	Ser Lys Met Ser Tyr Leu Gln Met Arg Asn Ser Gln Ala His Arg Asn		
	205	210	215 220
	Phe Leu Glu Asp Gly Glu Ser Asp Gly Phe Leu Arg Cys Leu Ser Leu		
	225	230	235
20	Asn Ser Gly Trp Ile Leu Thr Thr Thr Leu Val Leu Ser Val Met Val		
	240	245	250
	Leu Leu Trp Ile Cys Cys Ala Thr Val Ala Thr Ala Val Glu Gln Tyr		
	255	260	265
	Val Pro Ser Glu Lys Leu Ser Ile Tyr Gly Asp Leu Glu Phe Met Asn		
25	270	275	280
	Glu Gln Lys Leu Asn Arg Tyr Pro Ala Ser Ser Leu Val Val Val Arg		
	285	290	295 300
	Ser Lys Thr Glu Asp His Glu Glu Ala Gly Pro Leu Pro Thr Lys Val		
	305	310	315
30	Asn Leu Ala His Ser Glu Ile		
	320		

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<210> 29

<211> 827

<212> DNA

5 <213> Homo sapiens

<400> 29

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	Met Arg Arg Cys Ser Leu Cys	
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	gct ttc gac gcc gcc cgg ggg ccc agg cgg ctg atg cgt gtg ggc ctc	102
	Ala Phe Asp Ala Ala Arg Gly Pro Arg Arg Leu Met Arg Val Gly Leu	
	10 15 20	
	gcg ctg atc ttg gtg ggc cac gtg aac ctg ctg ctg ggg gcc gtg ctg	150
15	Ala Leu Ile Leu Val Gly His Val Asn Leu Leu Leu Gly Ala Val Leu	
	25 30 35	
	cat ggc acc gtc ctg cgg cac gtg gcc aat ccc cgc ggc gct gtc acg	198
	His Gly Thr Val Leu Arg His Val Ala Asn Pro Arg Gly Ala Val Thr	
	40 45 50 55	
20	ccg gag tac acc gta gcc aat gtc atc tct gtc ggc tcg ggg ctg ctg	246
	Pro Glu Tyr Thr Val Ala Asn Val Ile Ser Val Gly Ser Gly Leu Leu	
	60 65 70	
	agc gtt tcc gtg gga ctt gtg gcc ctc ctg gcg tcc agg aac ctt ctt	294
	Ser Val Ser Val Gly Leu Val Ala Leu Leu Ala Ser Arg Asn Leu Leu	
25	75 80 85	
	cgc cct cca ctg cac tgg gtc ctg ctg gca cta gct ctg gtg aac ctg	342
	Arg Pro Pro Leu His Trp Val Leu Leu Ala Leu Ala Leu Val Asn Leu	
	90 95 100	
	ctc ttg tcc gtt gcc tgc tcc ctg ggc ctc ctt ctt gct gtg tca ctc	390
30	Leu Leu Ser Val Ala Cys Ser Leu Gly Leu Leu Leu Ala Val Ser Leu	
	105 110 115	
	act gtg gcc aac ggt ggc cgc cgc ctt att gct gac tgc cac cca gga	438

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Thr Val Ala Asn Gly Gly Arg Arg Leu Ile Ala Asp Cys His Pro Gly
 120 125 130 135
 ctg ctg gat cct ctg gta cca ctg gat gag ggg ccg gga cat act gac 486
 Leu Leu Asp Pro Leu Val Pro Leu Asp Glu Gly Pro Gly His Thr Asp
 5 140 145 150
 tgc ccc ttt gac ccc aca aga atc tat gat aca gcc ttg gct ctc tgg 534
 Cys Pro Phe Asp Pro Thr Arg Ile Tyr Asp Thr Ala Leu Ala Leu Trp
 155 160 165
 atc cct tct ttg ctc atg tct gca ggg gag gct gct cta tct ggt tac 582
 10 Ile Pro Ser Leu Leu Met Ser Ala Gly Glu Ala Ala Leu Ser Gly Tyr
 170 175 180
 tgc tgt gtg gct gca ctc act cta cgt gga gtt ggg ccc tgc agg aag 630
 Cys Cys Val Ala Ala Leu Thr Leu Arg Gly Val Gly Pro Cys Arg Lys
 185 190 195
 15 gac gga ctt cag ggg cag gta gta gct ggg tgt gac gca aga gtg aaa 678
 Asp Gly Leu Gln Gly Gln Val Val Ala Gly Cys Asp Ala Arg Val Lys
 200 205 210 215
 cag aaa gcc tgg cag cca cgg ttt cct ggg att aaa gtc aaa gca tta 726
 Gln Lys Ala Trp Gln Pro Arg Phe Pro Gly Ile Lys Val Lys Ala Leu
 20 220 225 230
 tgaa tatggcacta aagtgactga gctaccagac caatgatcct gtaaggcagc 780
 cacagaacta aaaaacaaca attattatta aactgctctg gattctc 827

 <210> 30
 25 <211> 231
 <212> PRT
 <213> Homo sapiens

 <400> 30
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 1 5
 Ala Phe Asp Ala Ala Arg Gly Pro Arg Arg Leu Met Arg Val Gly Leu

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	25	30	35
	His Gly Thr Val Leu Arg His Val Ala Asn Pro Arg Gly Ala Val Thr		
5	40	45	50 55
	Pro Glu Tyr Thr Val Ala Asn Val Ile Ser Val Gly Ser Gly Leu Leu		
	60	65	70
	Ser Val Ser Val Gly Leu Val Ala Leu Leu Ala Ser Arg Asn Leu Leu		
	75	80	85
10	Arg Pro Pro Leu His Trp Val Leu Leu Ala Leu Ala Leu Val Asn Leu		
	90	95	100
	Leu Leu Ser Val Ala Cys Ser Leu Gly Leu Leu Leu Ala Val Ser Leu		
	105	110	115
	Thr Val Ala Asn Gly Gly Arg Arg Leu Ile Ala Asp Cys His Pro Gly		
15	120	125	130 135
	Leu Leu Asp Pro Leu Val Pro Leu Asp Glu Gly Pro Gly His Thr Asp		
	140	145	150
	Cys Pro Phe Asp Pro Thr Arg Ile Tyr Asp Thr Ala Leu Ala Leu Trp		
	155	160	165
20	Ile Pro Ser Leu Leu Met Ser Ala Gly Glu Ala Ala Leu Ser Gly Tyr		
	170	175	180
	Cys Cys Val Ala Ala Leu Thr Leu Arg Gly Val Gly Pro Cys Arg Lys		
	185	190	195
	Asp Gly Leu Gln Gly Gln Val Val Ala Gly Cys Asp Ala Arg Val Lys		
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	Gln Lys Ala Trp Gln Pro Arg Phe Pro Gly Ile Lys Val Lys Ala Leu		
	220	225	230

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30 <211> 1189

<212> DNA

<213> Homo sapiens

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<400> 31

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5	tagctgtgga accctagggg acctgttacc gcgctttggc gaaactgggt tcgctgctga	180
	tttgcgaaacc ttgacctgac ttctcaggc cttgagagat ctaagtaaatt ttggtggccc	240
	attgaaagga cctggagaga gcgtatgaag atctgcctct tctccaagaa actcaaccac	300
	tagtgaca atg acc agc ctc ctg act act cct tct cca aga gaa gaa ctg	350
	Met Thr Ser Leu Leu Thr Thr Pro Ser Pro Arg Glu Glu Leu	
10	1 5 10	
	atg acc acc cca att tta cag ccc act gag gcc ctg tcc cca gaa gat	398
	Met Thr Thr Pro Ile Leu Gln Pro Thr Glu Ala Leu Ser Pro Glu Asp	
	15 20 25 30	
	gga gcc agc aca gca ctc att gca gtt gtt atc acc gtt gtc ttc ctc	446
15	Gly Ala Ser Thr Ala Leu Ile Ala Val Val Ile Thr Val Val Phe Leu	
	35 40 45	
	acc ctg ctc tcg gtc gtg atc ttg atc ttc ttt tac ctg tac aag aac	494
	Thr Leu Leu Ser Val Val Ile Leu Ile Phe Phe Tyr Leu Tyr Lys Asn	
	50 55 60	
20	aaa ggc agc tac gtc acc tat gaa cct aca gaa ggt gag ccc agt gcc	542
	Lys Gly Ser Tyr Val Thr Tyr Glu Pro Thr Glu Gly Glu Pro Ser Ala	
	65 70 75	
	atc gtc cag atg gag agt gac ttg gcc aag ggc agc gag aaa gag gaa	590
	Ile Val Gln Met Glu Ser Asp Leu Ala Lys Gly Ser Glu Lys Glu Glu	
25	80 85 90	
	tat ttc atc taatgactcc caggccccaa ggagcttatt cctggctcca t	640
	Tyr Phe Ile	
	95	
	cgctaacacg ttgactgctt attatgggaa agttttctct gaagccaggg agaagcattg	700
30	attgatgtgg gcaaataccaa gctccagcca ggctgcagtc ccaaataccg acatcactga	760
	ctccagggac cagggacatg gagaaagctg tttatgatata ctttaaccag gccctottac	820
	tagagctggt gtttgtgact ggccaacaag atgtggctat gccaggggac atctgagtat	880

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gtgccagtc atcttttttc acagggtgaa gggagagaaa agattttgag ttaaggtcat 940
 tggetgctct actctgtccc ctacctggtc acctagtgat agccccagtg gagatactgt 1000
 ccatacaagg tcttcccaga ggctggatac cacagtaaaa ggccaggcca ggaggggtag 1060
 gagactatgg agatcttacc tcctgataaa tgtgctacac cccctaattct gagcccttcc 1120
 5 tttccgtgtt ccccaacaac ctcatgctta cgtgattttt attcaaatta aaaattttca 1180
 ttgctacag 1189

<210> 32

<211> 97

10 <212> PRT

<213> Homo sapiens

<400> 32

Met Thr Ser Leu Leu Thr Thr Pro Ser Pro Arg Glu Glu Leu
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 Met Thr Thr Pro Ile Leu Gln Pro Thr Glu Ala Leu Ser Pro Glu Asp
 15 20 25 30
 Gly Ala Ser Thr Ala Leu Ile Ala Val Val Ile Thr Val Val Phe Leu
 35 40 45
 20 Thr Leu Leu Ser Val Val Ile Leu Ile Phe Phe Tyr Leu Tyr Lys Asn
 50 55 60
 Lys Gly Ser Tyr Val Thr Tyr Glu Pro Thr Glu Gly Glu Pro Ser Ala
 65 70 75
 Ile Val Gln Met Glu Ser Asp Leu Ala Lys Gly Ser Glu Lys Glu Glu
 25 80 85 90
 Tyr Phe Ile
 95

<210> 33

30 <211> 1500

<212> DNA

<213> Homo sapiens

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<400> 33

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	gctccgggct gtgggaccgc tgggccccca gcg atg gcg acc ctg tgg gga ggc	114
5	Met Ala Thr Leu Trp Gly Gly	
	1 5	
	ctt ctt cgg ctt ggc tcc ttg ctc agc ctg tcg tgc ctg gcg ctt tcc	162
	Leu Leu Arg Leu Gly Ser Leu Leu Ser Leu Ser Cys Leu Ala Leu Ser	
	10 15 20	
10	gtg ctg ctg ctg gcg cag ctg tca gac gcc gcc aag aat ttc gag gat	210
	Val Leu Leu Leu Ala Gln Leu Ser Asp Ala Ala Lys Asn Phe Glu Asp	
	25 30 35	
	gtc aga tgt aaa tgt atc tgc cct ccc tat aaa gaa aat tct ggg cat	258
	Val Arg Cys Lys Cys Ile Cys Pro Pro Tyr Lys Glu Asn Ser Gly His	
15	40 45 50 55	
	att tat aat aag aac ata tct cag aaa gat tgt gat tgc ctt cat gtt	306
	Ile Tyr Asn Lys Asn Ile Ser Gln Lys Asp Cys Asp Cys Leu His Val	
	60 65 70	
	gtg gag ccc atg cct gtg cgg ggg cct gat gta gaa gca tac tgt cta	354
20	Val Glu Pro Met Pro Val Arg Gly Pro Asp Val Glu Ala Tyr Cys Leu	
	75 80 85	
	cgc tgt gaa tgc aaa tat gaa gaa aga agc tot gtc aca atc aag gtt	402
	Arg Cys Glu Cys Lys Tyr Glu Glu Arg Ser Ser Val Thr Ile Lys Val	
	90 95 100	
25	acc att ata att tat ctc tcc att ttg ggc ctt cta ctt ctg tac atg	450
	Thr Ile Ile Ile Tyr Leu Ser Ile Leu Gly Leu Leu Leu Leu Tyr Met	
	105 110 115	
	gta tat ctt act ctg gtt gag ccc ata ctg aag agg cgc ctc ttt gga	498
	Val Tyr Leu Thr Leu Val Glu Pro Ile Leu Lys Arg Arg Leu Phe Gly	
30	120 125 130 135	
	cat gca cag ttg ata cag agt gat gat gat att ggg gat cac cag cct	546
	His Ala Gln Leu Ile Gln Ser Asp Asp Asp Ile Gly Asp His Gln Pro	

35/45

	140	145	150	
	ttt gca aat gca cac gat gtg cta gcc cgc tcc cgc agt cga gcc aac	594		
	Phe Ala Asn Ala His Asp Val Leu Ala Arg Ser Arg Ser Arg Ala Asn			
	155	160	165	
5	gtg ctg aac aag gta gaa tat gca cag cag cgc tgg aag ctt caa gtc	642		
	Val Leu Asn Lys Val Glu Tyr Ala Gln Gln Arg Trp Lys Leu Gln Val			
	170	175	180	
	caa gag cag cga aag tct gtc ttt gac cgg cat gtt gtc ctc agc	687		
	Gln Glu Gln Arg Lys Ser Val Phe Asp Arg His Val Val Leu Ser			
10	185	190	195	
	taattgggaa ttgaattcaa ggtgactaga aagaaacagg cagacaactg gaa	740		
	agaactgact gggttttgct gggtttcatt ttaatacctt gttgatttca ccaactgttg	800		
	ctggaagatt caaaactgga agcaaaaact tgcttgattt ttttttcttg ttaacgtaat	860		
	aatagagaca tttttaaaag cacacagctc aaagtcagcc aataagtctt ttcctatttg	920		
15	tgacttttac taataaaaat aaatctgcct gtaaattatc ttgaagtcct ttacctggaa	980		
	caagcactct ctttttcacc acatagtttt aacttgactt tcaagataat tttcaggggtt	1040		
	tttggtggtg ttgttttttg tttgtttggt ttgggtgggag aggggagggg tgcctgggaa	1100		
	gtggttaaca acttttttca agtcacttta ctaaacaac ttttgtaaag agaccttacc	1160		
	ttctattttc gagtttcatt tatattttgc agtgtagcca gcctcatcaa agagctgact	1220		
20	tactcatttg acttttgac tgactgtatt atctgggtat ctgctgtgtc tgcacttcat	1280		
	ggtaaacggg atctaaaatg cctgggtggt tttcacaaaa agcagatttt cttcatgtac	1340		
	tgtgatgtct gatgcaatgc atcctagaac aaactggcca tttgctagtt tactctaaag	1400		
	actaaacata gtcttggtgt gtgtggtctt actcatcttc tagtaccttt aaggacaaat	1460		
	cctaaggact tggacacttg caataaagaa atttttatttt	1500		
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	<211> 198			
	<212> PRT			
	<213> Homo sapiens			
30	<400> 34			

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										1					5		
		Leu	Leu	Arg	Leu	Gly	Ser	Leu	Leu	Ser	Leu	Ser	Cys	Leu	Ala	Leu	Ser
				10						15					20		
5		Val	Leu	Leu	Leu	Ala	Gln	Leu	Ser	Asp	Ala	Ala	Lys	Asn	Phe	Glu	Asp
				25						30				35			
		Val	Arg	Cys	Lys	Cys	Ile	Cys	Pro	Pro	Tyr	Lys	Glu	Asn	Ser	Gly	His
				40				45					50				55
		Ile	Tyr	Asn	Lys	Asn	Ile	Ser	Gln	Lys	Asp	Cys	Asp	Cys	Leu	His	Val
10						60					65						70
		Val	Glu	Pro	Met	Pro	Val	Arg	Gly	Pro	Asp	Val	Glu	Ala	Tyr	Cys	Leu
					75						80					85	
		Arg	Cys	Glu	Cys	Lys	Tyr	Glu	Glu	Arg	Ser	Ser	Val	Thr	Ile	Lys	Val
				90						95					100		
15		Thr	Ile	Ile	Ile	Tyr	Leu	Ser	Ile	Leu	Gly	Leu	Leu	Leu	Leu	Tyr	Met
				105					110					115			
		Val	Tyr	Leu	Thr	Leu	Val	Glu	Pro	Ile	Leu	Lys	Arg	Arg	Leu	Phe	Gly
				120				125				130					135
		His	Ala	Gln	Leu	Ile	Gln	Ser	Asp	Asp	Asp	Ile	Gly	Asp	His	Gln	Pro
20						140					145					150	
		Phe	Ala	Asn	Ala	His	Asp	Val	Leu	Ala	Arg	Ser	Arg	Ser	Arg	Ala	Asn
				155						160					165		
		Val	Leu	Asn	Lys	Val	Glu	Tyr	Ala	Gln	Gln	Arg	Trp	Lys	Leu	Gln	Val
				170					175					180			
25		Gln	Glu	Gln	Arg	Lys	Ser	Val	Phe	Asp	Arg	His	Val	Val	Leu	Ser	
				185					190				195				

<210> 35

<211> 806

30 <212> DNA

<213> Homo sapiens

37/45

<400> 35

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gcctcagaga ccgcgcgcct tgtccccgag ggcc atg ggc cgg gtc tca ggg ctt 115

Met Gly Arg Val Ser Gly Leu

5 1 5

gtg ccc tct cgc ttc ctg acg ctc ctg gcg cat ctg gtg gtc gtc atc 163

Val Pro Ser Arg Phe Leu Thr Leu Leu Ala His Leu Val Val Val Ile

10 10 15 20

acc tta ttc tgg tcc cgg gac agc aac ata cag gcc tgc ctg cct ctc 211

Thr Leu Phe Trp Ser Arg Asp Ser Asn Ile Gln Ala Cys Leu Pro Leu

25 30 35

acg ttc acc ccc gag gag tat gac aag cag gac att cag ctg gtg gcc 259

Thr Phe Thr Pro Glu Glu Tyr Asp Lys Gln Asp Ile Gln Leu Val Ala

40 45 50 55

15 gcg ctc tct gtc acc ctg ggc ctc ttt gca gtg gag ctg gcc ggt ttc 307

Ala Leu Ser Val Thr Leu Gly Leu Phe Ala Val Glu Leu Ala Gly Phe

60 65 70

ctc tca gga gtc tcc atg ttc aac agc acc cag agc ctc atc tcc att 355

Leu Ser Gly Val Ser Met Phe Asn Ser Thr Gln Ser Leu Ile Ser Ile

20 75 80 85

ggg gct cac tgt agt gca tcc gtg gcc ctg tcc ttc ttc ata ttc gag 403

Gly Ala His Cys Ser Ala Ser Val Ala Leu Ser Phe Phe Ile Phe Glu

90 95 100

cgt tgg gag tgc act acg tat tgg tac att ttt gtc ttc tgc agt gcc 451

Arg Trp Glu Cys Thr Thr Tyr Trp Tyr Ile Phe Val Phe Cys Ser Ala

105 110 115

ctt cca gct gtc act gaa atg gct tta ttc gtc acc gtc ttt ggg ctg 499

Leu Pro Ala Val Thr Glu Met Ala Leu Phe Val Thr Val Phe Gly Leu

120 125 130 135

30 aaa aag aaa ccc ttc tgattacctt catgacggga acctaaggac gaagcc 550

Lys Lys Lys Pro Phe

140

38/45

	tacaggggca	agggccgctt	cgtattctctg	gaagaaggaa	ggcataggct	tcggttttcc	610
	cctcggaaac	tgcttctgct	ggaggatatg	tgttggaata	attacgtctt	gagtctggga	670
	ttatccgcac	tgtatttagt	gctttgtaat	aaaatatggt	ttgtagtaac	attaagactt	730
	atatacagtt	ttaggggaca	attgagatgg	ctgaactact	gaataaaaaa	aaaacaacgc	790
5	tgttttctag	tcctgc					806

<210> 36

<211> 140

<212> PRT

10 <213> Homo sapiens

<400> 36

[illegible]

39/45

<210> 37

<211> 1718

<212> DNA

5 <213> Homo sapiens

<400> 37

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	gct cct cgt cgc aat gaa gac ttt gtc ctc ctg ctc acc tac gtc ctc	98
	Ala Pro Arg Arg Asn Glu Asp Phe Val Leu Leu Leu Thr Tyr Val Leu	
	15 20 25	
	ttc ttg atg gcg ctg acc ttc ctc atg tcc tcc ttc acc ttc tgt ggt	146
15	Phe Leu Met Ala Leu Thr Phe Leu Met Ser Ser Phe Thr Phe Cys Gly	
	30 35 40 45	
	tcc ttc acg ggc tgg aag aga cat ggg gcc cac atc tac ctc acg atg	194
	Ser Phe Thr Gly Trp Lys Arg His Gly Ala His Ile Tyr Leu Thr Met	
	50 55 60	
20	ctc ctc tcc att gcc atc tgg gtg gcc tgg atc acc ctg ctc atg ctt	242
	Leu Leu Ser Ile Ala Ile Trp Val Ala Trp Ile Thr Leu Leu Met Leu	
	65 70 75	
	cct gac ttt gac cgc agg tgg gat gac acc atc ctc agc tcc gcc ttg	290
	Pro Asp Phe Asp Arg Arg Trp Asp Asp Thr Ile Leu Ser Ser Ala Leu	
25	80 85 90	
	gct gcc aat ggc tgg gtg ttc ctg ttg gct tat gtt agt ccc gag ttt	338
	Ala Ala Asn Gly Trp Val Phe Leu Leu Ala Tyr Val Ser Pro Glu Phe	
	95 100 105	
	tgg ctg ctc aca aag caa cga aac ccc atg gat tat cct gtt gag gat	386
30	Trp Leu Leu Thr Lys Gln Arg Asn Pro Met Asp Tyr Pro Val Glu Asp	
	110 115 120 125	
	gct ttc tgt aaa cct caa ctc gtg aag aag agc tat ggt gtg gag aac	434

40/45

	Ala Phe Cys Lys Pro Gln Leu Val Lys Lys Ser Tyr Gly Val Glu Asn	
	130 135 140	
	aga gcc tac tct caa gag gaa atc act caa ggt ttt gaa gag aca ggg	482
	Arg Ala Tyr Ser Gln Glu Glu Ile Thr Gln Gly Phe Glu Glu Thr Gly	
5	145 150 155	
	gac acg ctc tat gcc ccc tat tcc aca cat ttt cag ctg cag aac cag	530
	Asp Thr Leu Tyr Ala Pro Tyr Ser Thr His Phe Gln Leu Gln Asn Gln	
	160 165 170	
	cct ccc caa aag gaa ttc tcc atc cca cgg gcc cac gct tgg ccg agc	578
10	Pro Pro Gln Lys Glu Phe Ser Ile Pro Arg Ala His Ala Trp Pro Ser	
	175 180 185	
	cct tac aaa gac tat gaa gta aag aaa gag ggc agc taactctgtc ctgaag	630
	Pro Tyr Lys Asp Tyr Glu Val Lys Lys Glu Gly Ser	
	190 195 200	
15	agtgggacaa atgcagccgg gcggcagatc tagcgggagc tcaaagggat gtgggcgaaa	690
	tcttgagtct tctgagaaaa ctgtacaaga cactacggga acagtgtgcc tccctcccag	750
	cctcaaccac aattcttcca tgctggggct gatgtgggct agtaagactc cagttcttag	810
	aggcgctgta gtattttttt tttttttgtc tcatccttag gatacttctt ttaagtggga	870
	gtctcaggca actcaagttt agacccttac tctttttgtt tgttttttga aacaggatct	930
20	tgtctgtgca cccaggcttg agtgcagtgg tgcgatcaca gcccagtgca gcctcgacca	990
	cctgtgctca agcaatcctc ccatctccat ctcccaaagt gctgggatga caggcgtag	1050
	ccacagctcc cagcctaggc ccttaatctt gctgttatct tccatggact aaaggctctgg	1110
	tcatctgagc tcacgctggc tcacacagct ctaggggcct gctcctctaa ctacagtg	1170
	gttttgtgag gctctgtggc ccagagcaga cctgcatatc tgagcaaaaa tagcaaaagc	1230
25	ctctctcagc ccactggcct gaatctacac tggaagccaa cttgctggca cccccgctcc	1290
	ccaacccttc ttgcctgggt aggagaggct aaagatcacc ctaaatttac tcatctctct	1350
	agtgtgcct cacactgggc ctacagcagct cccagcacc aattcacagg tcaccctct	1410
	cttcttgac tgtcccaaaa cttgctgtca attccgagat ctaatctccc cctacgctct	1470
	gccaggaatt ctttcagacc tctactagcag aagcccggtt gctccttgctc aggagaattt	1530
30	gtacatcatt ctcaactcaa attcctgggg ctgatacttc tctcatcttg caccccaacc	1590
	tctgtaaata gatttacgc atttacggct gcattctgta agtgggcatg gtctccta	1650
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<211> 201

5 <212> PRT

<213> Homo sapiens

<400> 38

Met Asn Arg Thr Asn Val Asn Val Phe Ser Glu Leu Ser

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Ala Pro Arg Arg Asn Glu Asp Phe Val Leu Leu Leu Thr Tyr Val Leu

15 20 25

Phe Leu Met Ala Leu Thr Phe Leu Met Ser Ser Phe Thr Phe Cys Gly

30 35 40 45

15 Ser Phe Thr Gly Trp Lys Arg His Gly Ala His Ile Tyr Leu Thr Met

50 55 60

Leu Leu Ser Ile Ala Ile Trp Val Ala Trp Ile Thr Leu Leu Met Leu

65 70 75

Pro Asp Phe Asp Arg Arg Trp Asp Asp Thr Ile Leu Ser Ser Ala Leu

20 80 85 90

Ala Ala Asn Gly Trp Val Phe Leu Leu Ala Tyr Val Ser Pro Glu Phe

95 100 105

Trp Leu Leu Thr Lys Gln Arg Asn Pro Met Asp Tyr Pro Val Glu Asp

110 115 120 125

25 Ala Phe Cys Lys Pro Gln Leu Val Lys Lys Ser Tyr Gly Val Glu Asn

130

Arg Ala Tyr Ser Gln Glu Glu Ile Thr Gln Gly Phe Glu Glu Thr Gly

145 150 155

Asp Thr Leu Tyr Ala Pro Tyr Ser Thr His Phe Gln Leu Gln Asn Gln

30 160 165 170

Pro Pro Gln Lys Glu Phe Ser Ile Pro Arg Ala His Ala Trp Pro Ser

175 180 185

42/45

Pro Tyr Lys Asp Tyr Glu Val Lys Lys Glu Gly Ser

190

195

200

<210> 39

5 <211> 995

<212> DNA

<213> Homo sapiens

<400> 39

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	tgtctcccac gtccccccagg tgcgcggcca cc atg gcg tcc agc gac gag gac	173
	Met Ala Ser Ser Asp Glu Asp	
	1 5	
15	ggc acc aac ggc ggc gcc tcg gag gcc ggc gag gac cgg gag gct ccc	221
	Gly Thr Asn Gly Gly Ala Ser Glu Ala Gly Glu Asp Arg Glu Ala Pro	
	10 15 20	
	ggc aag cgg agg cgc ctg ggg ttc ttg gcc acc gcc tgg ctc acc ttc	269
	Gly Lys Arg Arg Arg Leu Gly Phe Leu Ala Thr Ala Trp Leu Thr Phe	
20	25 30 35	
	tac gac atc gcc atg acc gcg ggg tgg ttg gtt cta gct att gcc atg	317
	Tyr Asp Ile Ala Met Thr Ala Gly Trp Leu Val Leu Ala Ile Ala Met	
	40 45 50 55	
	gta cgt ttt tat atg gaa aaa gga aca cac aga ggt tta tat aaa agt	365
25	Val Arg Phe Tyr Met Glu Lys Gly Thr His Arg Gly Leu Tyr Lys Ser	
	60 65 70	
	att cag aag aca ctt aaa ttt ttc cag aca ttt gcc ttg ctt gag ata	413
	Ile Gln Lys Thr Leu Lys Phe Phe Gln Thr Phe Ala Leu Leu Glu Ile	
	75 80 85	
30	gtt cac tgt tta att gga att gta cct act tct gtg att gtg act ggg	461
	Val His Cys Leu Ile Gly Ile Val Pro Thr Ser Val Ile Val Thr Gly	
	90 95 100	

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	gtc caa gtg agt tca aga atc ttt atg gtg tgg ctc att act cac agt	509
	Val Gln Val Ser Ser Arg Ile Phe Met Val Trp Leu Ile Thr His Ser	
	105 110 115	
	ata aaa cca atc cag aat gaa gag agt gtg gtg ctt ttt ctg gtc gcg	557
5	Ile Lys Pro Ile Gln Asn Glu Glu Ser Val Val Leu Phe Leu Val Ala	
	120 125 130 135	
	tgg act gtg aca gag atc act cgc tat tcc ttc tac aca ttc agc ctt	605
	Trp Thr Val Thr Glu Ile Thr Arg Tyr Ser Phe Tyr Thr Phe Ser Leu	
	140 145 150	
10	ctt gac cac ttg cca tac ttc att aaa tgg gcc aga tat aat ttt ttt	653
	Leu Asp His Leu Pro Tyr Phe Ile Lys Trp Ala Arg Tyr Asn Phe Phe	
	155 160 165	
	atc atc tta tat cct gtt gga gtt gct ggt gaa ctt ctt aca ata tac	701
	Ile Ile Leu Tyr Pro Val Gly Val Ala Gly Glu Leu Leu Thr Ile Tyr	
15	170 175 180	
	gct gcc ttg ccg cat gtg aag aaa aca gga atg ttt tca ata aga ctt	749
	Ala Ala Leu Pro His Val Lys Lys Thr Gly Met Phe Ser Ile Arg Leu	
	185 190 195	
	cct aac aaa tac aat gtc tct ttt gac tac tat tat ttt ctt ctt ata	797
20	Pro Asn Lys Tyr Asn Val Ser Phe Asp Tyr Tyr Tyr Phe Leu Leu Ile	
	200 205 210 215	
	acc atg gca tca tat ata cct ttg ttt cca caa ctc tat ttt cat atg	845
	Thr Met Ala Ser Tyr Ile Pro Leu Phe Pro Gln Leu Tyr Phe His Met	
	220 225 230	
25	tta cgt caa aga aga aag gtg ctt cat gga gag gtg att gta gaa aag	893
	Leu Arg Gln Arg Arg Lys Val Leu His Gly Glu Val Ile Val Glu Lys	
	235 240 245	
	gat gat taaatgatct ctgcaaacaa ggtgcttttt ccagaataac caagattacc t	950
	Asp Asp	
30		
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44/45

<210> 40

<211> 249

<212> PRT

<213> Homo sapiens

5

<400> 40

Met Ala Ser Ser Asp Glu Asp

1

5

Gly Thr Asn Gly Gly Ala Ser Glu Ala Gly Glu Asp Arg Glu Ala Pro
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 Gly Lys Arg Arg Arg Leu Gly Phe Leu Ala Thr Ala Trp Leu Thr Phe
 25 30 35
 Tyr Asp Ile Ala Met Thr Ala Gly Trp Leu Val Leu Ala Ile Ala Met
 40 45 50 55
 15 Val Arg Phe Tyr Met Glu Lys Gly Thr His Arg Gly Leu Tyr Lys Ser
 60 65 70
 Ile Gln Lys Thr Leu Lys Phe Phe Gln Thr Phe Ala Leu Leu Glu Ile
 75 80 85
 Val His Cys Leu Ile Gly Ile Val Pro Thr Ser Val Ile Val Thr Gly
 20 90 95 100
 Val Gln Val Ser Ser Arg Ile Phe Met Val Trp Leu Ile Thr His Ser
 105 110 115
 Ile Lys Pro Ile Gln Asn Glu Glu Ser Val Val Leu Phe Leu Val Ala
 120 125 130 135
 25 Trp Thr Val Thr Glu Ile Thr Arg Tyr Ser Phe Tyr Thr Phe Ser Leu
 140 145 150
 Leu Asp His Leu Pro Tyr Phe Ile Lys Trp Ala Arg Tyr Asn Phe Phe
 155 160 165
 Ile Ile Leu Tyr Pro Val Gly Val Ala Gly Glu Leu Leu Thr Ile Tyr
 30 170 175 180
 Ala Ala Leu Pro His Val Lys Lys Thr Gly Met Phe Ser Ile Arg Leu
 185 190 195

45/45

Pro Asn Lys Tyr Asn Val Ser Phe Asp Tyr Tyr Tyr Phe Leu Leu Ile
200 205 210 215
Thr Met Ala Ser Tyr Ile Pro Leu Phe Pro Gln Leu Tyr Phe His Met
220 225 230
5 Leu Arg Gln Arg Arg Lys Val Leu His Gly Glu Val Ile Val Glu Lys
235 240 245
Asp Asp